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may lead to a better understanding of many phases of the mechanisms that are operative in the region of the perforation. The precise effects of gastric suction are not established. Its major influence may be that of effectively retarding reperforation of self-sealing perforations rather than that of determining the spontaneous closure. On the basis of presently published results there is adequate evidence to imply that most peptic ulcer perforations seal spontaneously. When emergency surgery is performed in order to accomplish simple closure of perforated ulcer, the surgeon often unavoidably destroys the sealing before visualizing the perforation. It may well be that his observations are inherently inadequate as a method of learning the frequency of spontaneous closure.

If gastric aspiration is viewed as a method for the demonstration of self-sealing, but by itself therapeutically unacceptable because of a lack of positivity, a precise method for the demonstration of sealing could lead to the conservative treatment of many cases of perforation now being treated by surgery. Emergency roentgenographic study following the instillation of gastrografin into the stomach may provide a positive means of establishing the presence or absence of leakage. This could make possible an important expansion of the concept of forme fruste perforation. At present the forme fruste perforation is recognized by the presence of minimal signs of peritoneal irritation in association with demonstrable spontaneous pneumoperitoneum. The implied presence of self-sealing is inherent in this diagnosis. The preferential use of gastric suction in operable cases of perforation implies the same concept in the presence of severe peritoneal irritation, and would be reasonable if self-closure of the perforation could be proved initially.

Further reduction in the mortality rate from gastroduodenal perforation involves refinement of many details of treatment. Laparotomy and simple closure have been shown to be applicable with almost no mortality in the otherwise healthy patient whose perforation is very recent. In those patients whose perforations have existed long enough to have produced serious peritoneal injury there are serious systemic consequences. The most important is hypovolemic shock aggravated by poor pulmonary ventilation and infection. Shock is probably the most often overlooked and the most lethal mechanism resulting from perforation. The usual urgency attached to the supposed need for closing the perforation before twelve hours has elapsed impairs recognition and treatment of the shock. This is especially true if the shock is still compensated. Since the shock of perforation is primarily due to plasma loss into the injured area and since the resultant hemoconcentration is easily demonstrated, an unusually simple means of measuring the shock mechanism is available by measuring the blood hemoglobin concentration. As clinical evidences of shock, the blood pressure taken in the sitting position and the renal excretion rate should be carefully interpreted. With these three guides, and the knowledge that plasma losses will inevitably exist in proportion to the degree of peritoneal injury, repletion requirements should be clearly apparent. Concurrent use of gastric suction will minimize any further peritoneal injury. With the patient in the decubitus position, left side down, the gastroduodenal loop is vertical and any tendency toward perforation leakage is further reduced. These latter measures make deliberate preparation of the patient for surgery feasible. Such preparation is the most important single feature of the management of individual cases.

The hypoxic effects of hypovolemia are importantly aggravated by impaired pulmonary mechanical activity. This is more severe in perforated ulcer than in any other known condition, reaching an 80 per cent reduction in mechanical pulmonary efficiency. The mechanism of this reduced function is closely related to, and is greatly aggravated by, the similar severe effects of an upper midline abdominal incision. The resultant hypoxemia adds to the tissue hypoxia produced by the shock. Early reduction of pain, with minimal incidental depression of the respiratory center, is therefore of extreme importance in the correction of the shock. Effective drugs are now available to neutralize the respiratory depressant action of narcotics.

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Surgical Technic

As one recapitulates the major advances in surgical therapy during the past few decades, the role of surgical technic in the operating room deserves re-emphasis. Many of the advances or extensions of surgical procedures have been made possible through contributions outside the discipline of surgery. Today, with vastly improved pre- and postoperative care, many of the complications of surgery can be ascribed purely to errors in operative technics or judgment.

Anesthesia, asepsis, blood typing, the nature of the internal environment, more complete understanding of the role of nutrition, antibiotics, blood banks, blood fractions, increased knowledge of surgical physiology, better instruments, better suture materials, and an appreciation of the local and systemic response to trauma, indicate a number of the major areas of advance. It is possible today for the poorly trained or inept surgeon to "get away" with many procedures that would never have been attempted in past decades. Residents in training are aided and supported more often in their judgment than in their specific technics, and often the authority to operate on a patient is considered a right instead of a privilege.

Lack of appreciation of, or disrespect for, living tissue and the local response to trauma, will result in minor and major complications. The animal laboratory is emerging, fortunately, as a rightful area for periods of rotation, research and technical training. The basic principles of surgical technic are simple and have been depicted and described by Halsted a half century ago. The importance of asepsis, hemostasis, blood supply to parts, approximation of tissue, obliteration of dead spaces, and avoidance of tissue tension, is quickly emphasized as such causes of failures are readily apparent. The great and more subtle variable among surgeons is gentleness in the broad and specific aspects of handling living tissue. This includes the use of hands and instruments as well as the varying techniques of sharp and blunt dissection. Roughness, mass ligatures, inept dissection technics, all contribute to local cellular damage, edema, transudation, bleeding, hemorrhage, and infection. When wound healing procedes normally, many postoperative complications are minimized. Perhaps the statement of a well known surgeon did not indicate egotism when he said that he attempted to prevent many postoperative complications in the operating room.

It behooves the attending staff to be scrupulous in this area of training of younger surgeons. Occasionally, the senior surgeon should evaluate critically his own technic.

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Enzymatic Débridement with Bovine Fibrinolysin

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Enzymatic débridement is a feasible and rational adjunct to the treatment of infected wounds. Various chemical agents capable of facilitating the débridement of ulcerating surfaces have been available for a number of years. Their use as substitutes for or adjuncts to operative removal of undesirable necrotic tissue, fibrin and bacterial debris has been proposed because they attack non-viable tissue selectively and permeate to areas relatively inaccessible to local removal by a limited operation.

The characteristics of an ideal agent or combination of agents for débridement should include: (1) a sufficiently broad spectrum of activity, capable of removing all forms of necrotic tissue; (2) no injurious effect on living tissue; (3) no irritating or pyrogenic effects; (4) sufficient duration of activity so that repeated applications at short intervals are not necessary; and (5) a reasonable cost to the patient.

An agent, or more likely, combination of agents having all of these properties does not yet exist. A number of enzymes or enzyme activators have been evaluated [*1–7*], but none has obtained widespread use for the débridement of superficial ulcerating surfaces.

Trypsin is an active proteolytic enzyme which is effective in débriding some forms of necrotic tissue but its short duration of activity and irritating side effects have limited its usefulness; it has also been claimed that trypsin inhibitors will develop after repeated treatment [*6*]. Papain is another proteolytic enzyme effective in wound débridement. It too produces pain and skin irritation, and there is some presumptive evidence that its activity may also affect some living cells [*8*]. Streptokinase is an enzyme activator rather than an active enzyme in itself. It activates profibrinolysin (plasminogen) in serum to the active proteolytic enzyme fibrinolysin (plasmin). Serum must be present in sufficient quantity to obtain an effective concentration of fibrinolysin; in addition, streptokinase may produce pyrogenic reactions of considerable severity. More recently, preparations of fibrinolysin itself or of profibrinolysin plus streptokinase have been used [*6*]; this is a more rational approach since it is possible to supply active enzyme in sufficient quantity to produce an adequate proteolytic effect. However, preparations of fibrinolysin from human sources have been very expensive. Bovine fibrinolysin has also been prepared and seems to be equally effective in human beings. Bovine pancreatic desoxyribonuclease is also available; this enzyme is effective in lysing desoxyribonucleic acid present in leukocytes and other nuclear debris. Several other proteolytic enzymes from both plant and bacterial sources have had a limited experimental trial but sufficient information is not yet available to evaluate their effectiveness, side effects, etc.

One of the deficiencies in all of these enzyme preparations is that none is really adequate in lysing dense dead collagenous eschar, such as one sees in third degree burns and in some

chronic superficial ulcers. A good non-pyrogenic collagenase and elastase would be of real value in more effectively attacking this fundamental problem in enzymatic débridement.

This study is an attempt to evaluate the effectiveness of bovine fibrinolysin with and without bovine pancreatic desoxyribonuclease in both lyophilized and ointment form in the management of superficial ulcerating lesions. An ideal type of experimental design could not be used because each wound presents a separate problem in healing. So many local and systemic factors influence wound healing that it was not believed that a double blind type of study could be designed to yield valid data.

MATERIAL AND METHODS

Bovine fibrinolysin was prepared by the method of Loomis, George and Ryder [9]. Desoxyribonuclease was extracted in non-crystalline form from bovine pancreas. Both were supplied as lyophilized powder or in a water-free ointment base.* Graduated concentrations of fibrinolysin (25 to 100 Loomis units/vial) and desoxyribonuclease (7,500 to 25,000 units/vial) were used in an attempt to assess the concentration necessary for optimal débridement. The ointment preparation contained 35 units of fibrinolysin and 15,000 units of desoxyribonuclease in 15 gm. of an anhydrous modified petrolatum base. The ointment vehicle was utilized to attain optimal concentration of enzyme at a local area while minimizing the evaporation and loss present when lyophilized enzyme was reconstituted and used as a wet dressing.

Patients were selected who had failed to obtain satisfactory débridement by operative or other conservative means. Almost all of these patients had been treated with saline, hydrogen peroxide or acetic acid soaks for one week to several months prior to the trial of enzymatic débridement. Lyophilized preparations were diluted with the minimal amounts of 0.9 per cent saline solution necessary to saturate a dressing or eye pad (in the case of small ulcers) placed in the wound. This dressing was covered with additional dressings and oiled silk to minimize evaporation. Dressings were kept in place for three hours; then the wound was air-dried for one hour and another enzyme application was made. The enzyme solutions were usually applied three times daily. The ointment preparations were used in a similar manner; a thin layer of ointment was applied for periods of three hours, followed by saline wet dressings to remove the ointment base, air-drying, and then another application. The usual course of treatment for the preparation of infected ulcerations for grafting was two to five days. When grafting procedures were not contemplated, longer courses of treatment were used.

The investigators deliberately attempted to divorce themselves from any attempt to assess the results of the treatment program. Members of the resident staff, most of whom were highly skeptical of the value of enzymatic débridement, were told that a brief course of enzymatic débridement was to be tried and were asked to write their opinions as to the results obtained in the progress notes. In addition, close-up color photographs were taken of all wounds prior to and following enzymatic débridement for comparison by a disinterested observer who had nothing to do with the treatment of these patients.

RESULTS

Fifty patients with chronic ulcerating lesions of the skin were treated with fibrinolysin. Classification of the types of lesion treated is difficult, but they have been grouped into the following gross categories.

Abscess Cavities and Infected Operative Wounds (Eight Patients). Six of these lesions were uncomplicated, while two were associated with osteomyelitis. All were infected and satisfactory granulation tissue had failed to develop following operative débridement and/or saline, acetic acid or bacitracin wet dressings. Of the six wounds uncomplicated by osteomyelitis, three healed by secondary intention while under treatment with fibrinolysin and desoxyribonuclease. A clean granulating base developed in the other three which were closed successfully by excision and primary closure (two cases) or by split thickness skin grafting (one case).

The two wounds associated with osteomyelitis improved, but complete healing was not attained.

Ulcerations Associated with Arteriosclerotic Peripheral Vascular Insufficiency (Sixteen Patients). Since arteriosclerotic ulcers do not respond well to any form of therapy, it is not surprising that little long-term improvement

* Supplied as Elase by the Department of Clinical Investigation, Parke, Davis and Co., Detroit, Michigan.

was observed following fibrinolysin débridement. Six ulcers failed to show significant improvement; the presence of exposed necrotic collagenous tissue precluded any effect from enzymes active against fibrin or nucleic acid substrates. Seven ulcers were satisfactorily débrided, but subsequent healing did not occur.

Three ulcers improved markedly. Two of these ulcerations of the foot were in diabetics with peripheral arterial disease in whom trauma and infection may have been more important than a decrease in arterial blood supply. One showed measurable progressive healing after two weeks of treatment with the combined enzymes in the ointment base. The remaining two ulcers were successfully grafted with split thickness skin after fibrinolysin débridement for four and six days respectively.

Trophic Ulcers (*Three Patients*). All of these patients had paraplegia with true trophic ulcers of the lower extremities. Débridement was effective in all three; in two, slow progressive healing took place on this regimen alone. The third patient had a malleolar ulcer which improved after four days of treatment; application of a split thickness skin graft was 100 per cent successful.

Decubitus Ulcers (*Seven Patients*). All of this group had ulcers which had failed to respond to weeks of saline and hydrogen peroxide soaks. Each ulcer showed considerable improvement after three to six days of treatment with fibrinolysin. Three, however, required subsequent operative débridement of dead collagen. All ulcerations ultimately healed. One ulcer required a pedicle graft. The others healed spontaneously or following operative closure in periods of two weeks to three months.

Stasis Ulcers (*Five Patients*). Four patients showed rapid and marked improvement with one to nine days of enzymatic débridement. Two of the ulcers healed spontaneously and two were successfully grafted with split thickness skin. The fifth ulcer had been present for nine years and failed to show significant improvement after five days of fibrinolysin therapy; after the ulcer was excised, microscopic examination demonstrated dense scar tissue extending through the deep fascia.

Burns (*Four Patients*). These four patients had chronically infected second and third degree burns which had failed to respond to prolonged treatment with intermittent saline soaks. All were treated with the topical ointment concontaining both fibrinolysin and desoxyribonuclease. The two patients with third degree burns had a rapid and excellent response to treatment in four to six days; skin grafts were successfully applied. The other two patients with deep second degree burns were treated for seven and twenty-five days respectively with complete epithelialization without grafting.

Miscellaneous Ulcerative Lesions (*Seven Patients*). One patient with psoriasis had an ulcer of indeterminate etiology over the lower part of the leg which had failed to respond to the usual conservative regimen but healed rapidly after enzymatic débridement of its fibrinopurulent base.

Another patient had a 3 by 6 cm. area of skin necrosis in the antecubital space following subcutaneous extravasation of bromsulphalein dye. Two and a half weeks of saline and hydrogen peroxide soaks failed to improve the dirty granulating ulcer. Ten days of fibrinolysin-desoxyribonuclease ointment applications resulted in considerable improvement and at the end of this period a split-thickness skin graft was successfully applied to the flat healthy granulating base of the ulcer.

A gangrenous ulcer of the great toe secondary to thromboangiitis obliterans in a thirty-nine year old man was too infected to permit local amputation. After five days of enzymatic débridement, amputation of the toe was performed and the wound healed primarily.

A sixty year old alcoholic with extensive frostbite of both feet had bilateral infected ulcers of both heels which had failed to respond satisfactorily after three weeks of saline and acetic acid soaks. After three days of enzymatic débridement, split thickness skin graft was applied and an 80 per cent take obtained.

Three years prior to this study a large necrotic ulcer of the lower abdominal wall developed in a forty-three year old man in an area which had received radiation for a neoplasm of the bladder. Repeated pedicle grafts to the area had failed because of persistent infection and local vascular insufficiency. One week of treatment with fibrinolysin soaks resulted in considerable improvement in the ulcer base and the first signs of peripheral epithelialization.

A patient with a chronic draining sinus of the heel communicating with a post-traumatic osteomyelitis of the os calcis failed to show any

noticeable improvement with four days of fibrinolysin-desoxyribonuclease therapy.

A seventeen year old student with a 6 cm. open wound subsequent to excision of a pilonidal cyst eleven months before was treated with fibrinolysin-desoxyribonuclease ointment for twenty-two days during which time complete healing occurred.

COMMENTS

Unfortunately a study of this sort must depend primarily on a subjective interpretation of results. We were unable to conceive an entirely objective type of evaluation. Each wound is an individual problem with regard to rate of healing, extent of infection, the body's response to that infection, types of contaminating organisms, etc. Infection of ulcerative surfaces is one of the major factors which delay healing or prevent definitive operative correction of these defects. Since fibrinous debris serves as one of the chief sources of nutrition furthering continued bacterial proliferation in open wounds, there is a good reason for elimination of fibrin and other protein debris. Facilitation of wound débridement should play a role in reduction of superficial infection. This in turn might be expected to have a secondary effect on the rate of wound healing.

Extensive *in vitro* studies with the fibrinolysin enzyme system have been carried out in this laboratory in the past. The effects of temperature, pH, electrolyte concentrations and serum inhibitors on enzyme activity and stability have been evaluated. An effort has been made to use as much of this information as possible in the practical utilization of this enzyme in wound débridement. The primary substrate on which this enzyme acts is fibrin. However, in higher concentrations, it also has hydrolytic effects on fibrinogen and other proteins.

The desoxyribonucleic acid arising from the dead leukocytes in purulent material led to the inclusion of desoxyribonuclease in the enzyme preparation. Theoretically, hydrolysis of this protein material as well would be advantageous. As far as this study was concerned, there was no way to assess accurately the effects on débridement produced by the inclusion of desoxyribonuclease. It was our impression that the addition of this enzyme proved desirable since a number of wounds heavily contaminated with purulent material and unresponsive to prior therapy cleared up rapidly coincident with the application of the combined enzyme preparation.

Previously, Spier, Rees and Clifton [*6*] have reported that streptokinase-activated human profibrinolysin is effective in débriding ulcerating surfaces. The active bovine fibrinolysin utilized in this study presents certain possible advantages relative to the greater ease in procurement and lesser cost of bovine plasma as compared to human plasma. In addition, the pyrogenic reactions which occasionally occur with the use of streptokinase are eliminated.

What are the therapeutic results and possible advantages of enzymatic débridement with fibrinolysin-desoxyribonuclease? This is not a "wonder drug" which will accomplish the impossible. However, in certain cases, definite improvement in the appearance of infected ulcers was achieved following the application of these enzymes. Ulcerations selected for this study were those which had failed to respond, even after weeks, to the usual conservative measures of saline, hydrogen peroxide or acetic acid soaks. Effective débridement was obtained with this preparation in a significant proportion of these refractory cases. Furthermore, more rapid preparation of an infected, ulcerated surface for grafting or secondary closure is a real economic advantage in this time of increasing cost of hospital care.

Failures were expected and were encountered in those ulcers containing significant amounts of dead collagen. We know of no clinically available enzyme preparation having a significant effect on dense collagenous eschar. In the absence of an effective collagenase, operative débridement is the best approach for removal of this tissue.

The ultimate prognosis for healing or for graft survival depends primarily on the nature and extent of the underlying disease. Probably the poorest over-all response was seen in the group of patients having lesions complicated by underlying arterial insufficiency. There is no therapy that achieves very significant results in healing arteriosclerotic ulcers. Even if one accomplishes excellent débridement of an ulcer surface, there is little likelihood that an ulcerated area secondary to a grossly deficient arterial blood supply will heal under any circumstances. Interestingly enough, several patients with extremely painful arterial ulcers had marked relief of pain following enzymatic débridement with subsidence of the associated infection and inflammation even though the

ulcer showed no evidence of healing. As might be expected, the most satisfactory results in this group were achieved in several patients with the diabetic type of peripheral vascular disease in which trauma and poor response to infection probably played a greater role in causing persistence of the ulcer than did the associated peripheral vascular insufficiency.

Similarly, the notoriously poor healing capability of paraplegics with decubitus ulcers influences the effectiveness of débridement accomplished by any means. The use of this preparation can be expected to lyse fibrin and nuclear debris but complementary operative removal of dead collagen and elastic tissue may also be necessary.

After the dense black eschar has been removed, aid in the preparation of chronically infected third degree burns for grafting may be obtained with fibrinolysin. In addition, it has been very pleasing to see rapid healing of extensively infected second degree burns after the infection had cleared coincident with enzymatic débridement.

Optimal results can be expected in those patients with simple infected wounds or ulcers uncomplicated by arterial insufficiency, radiation change, large amounts of dead collagenous tissue or dense scar. In these instances, one can expect almost uniformly rapid and effective preparation of the wound for grafting, secondary closure, or for spontaneous epithelialization.

Except in deep, irregular abscess cavities, the preparation of choice will probably prove to be a combination of fibrinolysin and desoxyribonuclease in a water-miscible ointment base. The advantage is essentially an economic one. Much larger quantities of reconstituted lyophilized enzyme are required to maintain optimal enzyme concentration in wet dressings applied to the wound. *In vitro* studies suggest that once active fibrinolysin has been in contact with water, maximal enzymatic activity has dissipated by the end of a three-hour period. It is easy to remove the ointment base with saline wet dressings and then apply another layer of ointment. Utilization of enzyme-containing ointment rather than the lyophilized preparation results in a ten-fold reduction in cost. There seems to be no significant difference in effectiveness of these preparations as long as one can technically achieve adequate coverage of the wound surface with the ointment. Satisfactory results have also been achieved with outpatient therapy. No side reactions or irritation have been noted.

SUMMARY

Bovine fibrinolysin, alone or in combination with desoxyribonuclease, appears to be of value in the enzymatic débridement of ulcerating wounds. This agent achieved more rapid and frequently more effective superficial débridement of a significant proportion of ulcerating surfaces which had failed to respond satisfactorily to other forms of local care. This is not a miracle drug, but it can be considered a useful adjunct in the preparation of a dirty or infected ulcerative surface for grafting, secondary closure or spontaneous epithelialization.

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A Simple Method for the Determination of Aortic Valve Gradients at Surgery

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THE determination of pressure gradients across a stenotic valve at the time of surgery enables the surgeon to assess his results at a time when further treatment is possible. However, any technique employed in the operating room should be as simple as possible to avoid confusion and misinterpretation. Comparison of the ventricular and aortic systolic peak pressures furnishes a workable approach to aortic stenosis if the gradient is reproducible. To facilitate this we have employed a Y tube device with a three-way stopcock to bridge the aortic valve. The bridge is balanced as a unit with an identical zero point for both ventricle and aorta. Pressures are sensed by a strain-gauge manometer connected to one channel of a standard recorder. By alternating the stopcock, consecutive ventricular and aortic pressures are recorded graphically for immediate analysis.

MATERIAL AND METHODS

The Y bridge (Fig. 1) has been constructed from a three-way tubing stopcock (BD No. 1022/s). The stopcock must fit tightly to assure undamped recording. A No. 16 Luer lock needle hub is silver soldered to one limb of the stopcock for direct connection with the strain gauge. Six-inch lengths of vinyl tubing (American Instrument Co., No. 5–8966, ⅛ inch O. D., 1/16 inch I. D.) are drawn over the other two limbs of the stopcock. Transparent tubing aids in clearing the system of air bubbles. The distal end of the tubing is attached to male Luer lock adapters (BD No. H/468 L) and No. 22 needles are connected for direct puncture. Any recording unit and any strain gauge which can be sterilized can be employed (we are currently using a P 23 D Sattham gauge with a Grass Polygraph six-channel recorder).

At operation the pericardium is incised over the left ventricle and aorta in preparation for transventricular commissurotomy. The strain gauge and bridge are filled with dilute heparin solution (1 mg./cc.) and meticulously freed of air bubbles. A small area of the ascending aorta is denuded of adventitia to prevent subsequent formation of hematoma. After the strain gauge has been balanced and calibrated, the needles are inserted into the left ventricle and aorta. Tracings for contour and ventricular end

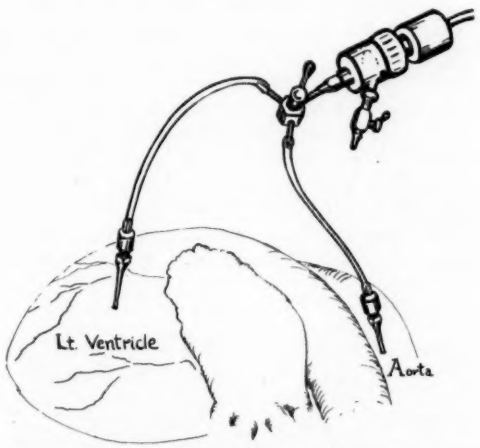

FIG. 1. Schematic drawing of Y bridge. Alternating stopcock permits recording of consecutive pressure tracings from ventricle and aorta.

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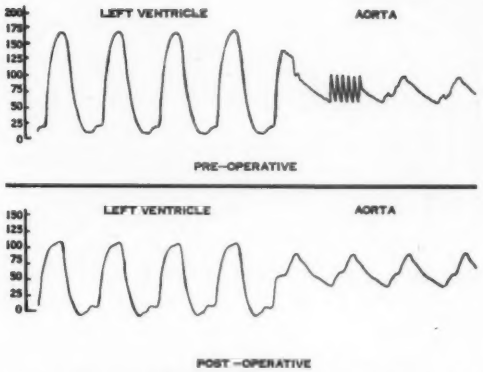

FIG. 2. Tracings obtained at 25 mm./sec. paper speed for contour and ventricular end-diastolic pressure.

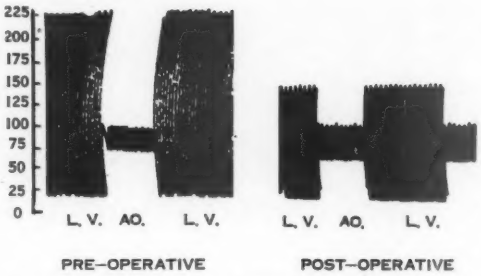

FIG. 3. Graphic picture of systolic peak gradient obtained at 1 mm./sec. paper speed and alternation between ventricle and aorta.

diastolic pressure are recorded at 25 mm./sec. paper speed. (Fig. 2.) The paper speed is then slowed to 1 mm./sec. and consecutive ventricular and aortic pressures are recorded during controlled respiration and apnea. The systolic peak gradient can be read directly. (Fig. 3.) Occasionally during aortic commissurotomy it is necessary to split-dilate the valve two or three times before the gradient is satisfactorily reduced. Pressure studies are made after each dilatation until the optimal hemodynamic response is obtained. When the intracardiac procedure has been completed, the heart is allowed to adjust to the new dynamics and a final series of pressures is recorded. (Figs. 2 and 3.)

COMMENTS

There has been considerable speculation and disagreement over the years about the value of pressure determinations at operation for stenotic valvular lesions. Many have contended that the gradients during surgery are unreliable because of anesthesia, the open chest and diminished cardiac output. Correlation of data obtained on our service by comparing preoperative cardiac catheterization with that during operation (in two series of patients with aortic and pulmonic stenosis) does not support these contentions. The average systolic peak gradient across the aortic valve in sixteen con-

TABLE I
AORTIC STENOSIS*

Patient	Preoperative Levels			Operative Levels		
	Gradient	Left Ventricle	Aorta	Gradient	Left Ventricle	Aorta
T. T.	70	170	100	114	230	116
T. A.	100	200	100	110	250	140
L. W.	120	230	110	112	220	108
J. W.	60	160	100	115	280	165
L. D.	60	168	108	24	110	86
E. L.	78	190	112	80	150	70
A. S.	115	230	115	75	175	100
M. S.	80	220	140	70	165	95
C. R.	84	220	136	60	170	110
L. D.	78	200	122	50	140	90
H. B.	50	180	130	55	175	120
W. S.	40	260	220	40	215	175
C. W.	55	220	165	40	215	175
M. S.	148	240	92	135	235	100
H. S.	65	190	125	75	185	110
A. G.	60	200	140	50	175	125
Average	79	205	126	75	193	118

* Systolic peak pressures.

TABLE II
PULMONIC STENOSIS*

Patient	Preoperative Levels			Operative Levels		
	Gradient	Right Ventricle	Pulmonary Artery	Gradient	Right Ventricle	Pulmonary Artery
K. S.	80	100	20	95	115	20
A. C.	65	80	15	75	95	20
K. N.	108	120	12	80	120	40
D. T.	155	168	13	108	120	12
K. H.	100	130	30	110	150	40
B. G.	172	200	28	132	160	28
J. E.	68	96	28	104	120	16
J. A.	82	92	10	110	120	10
K. W.	130	144	14	130	150	20
K. M.	66	76	10	27	47	20
D. F.	90	105	15	90	105	15
L. S.	111	136	25	90	108	18
T. S.	220	240	20	200	225	25
B. K.	89	104	15	85	100	15
A. W.	100	120	20	65	95	30
Average	109	127	18	100	122	22

* Systolic peak pressures.

secutive patients undergoing catheterization of the left side of the heart was 79 mm. Hg. The average operative gradient for these same patients was 75 mm. Hg. (Table I.) Similarly fifteen consecutive patients with pulmonic stenosis had an average systolic peak gradient of 109 mm. Hg during preoperative catheterization of the right side of the heart and 100 mm. Hg on the operating table prior to valvotomy. (Table II.) It is important to appreciate that even though the preoperative and operative gradients may vary somewhat for an individual case, this variation is not systematic and tends to cancel out when an entire series is analyzed. Data obtained from the sixteen patients with aortic stenosis showed a moderate decrease of both ventricular and aortic pressures at surgery, but the gradient was not markedly altered. It is known that cardiac output is lower during thoracic surgery. The small change in gradient, however, may be a reflection of the simultaneous decrease of peripheral resistance. Even in the series of patients with pulmonic stenosis, however, when pulmonary arterial pressures and probably pulmonary vascular resistances were slightly elevated during operation, there was no striking discrepancy between the gradients.

If then, as these studies would indicate, the values are not meaningless, operative gradients offer a valuable adjunct for determining the completeness of the surgical procedure at a time when further manipulation is possible. The described method for graphic recording of aortic valve gradients permits rapid, uncomplicated interpretation which has been helpful during surgery. This technique is also applicable to other stenotic lesions.

SUMMARY

1. A simple Y bridge is described which facilitates the determination of pressure gradients across the aortic valve during surgery.

2. Comparison of preoperative and operative gradients in patients with aortic and pulmonic stenosis has shown satisfactory correlation, enhancing the value of operative pressure studies.

Original Signs and Symptoms in Patients Surviving Five Years after Atomic Bomb Exposure under 1,000 Meters

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NUMEROUS reports have been published reviewing the signs and symptoms of atomic bomb victims [1–5]. These reports, although dealing many times with the same patients, approached the medical aspects from different viewpoints. Subsequently, other investigators re-evaluated again the dreadful events and consequences of that clear August morning in 1945 [6–8]. The reasons for the intense interest in the early complaints of the victims are obvious: a new disease syndrome; the specter of malignancies, blood dyscrasias and genetic mutations; flash burns due to unrivaled intensities of radiant heat; and the evaluation of a new weapon of warfare and a new source of energy for peaceful purposes.

This report deals only with survivors who were exposed 1,000 meters or less from the hypocenter in Hiroshima and were living at least five years after the dropping of the atomic bomb. Although a thermonuclear weapon was detonated in March, 1954, at Bikini Isle, it does not render obsolete the findings in the population of Hiroshima following the atomic bomb explosion. With a thermonuclear weapon the scale of injuries will be many times greater, but the types of injuries will be similar. If in the future another wide conflict occurs, atomic weapons as well as thermonuclear weapons will be used. The information in this paper, therefore, may be of some aid to civilian defense groups as well as physicians.

HISTORY

The Hiroshima bomb was detonated at an altitude of approximately 580 meters at 8:15 A.M. on August 6, 1945. Immediately many Japanese scientists began making mental notes of what happened to them and to the hordes of patients arriving at the temporary clinics and first-aid stations [9]. About forty-eight hours later the first Japanese investigating teams arrived in the chaotic city. These teams were from the huge scientific centers, such as Tokyo, Kyoto, Osaka, Okayama and Kyushu. Their brilliant work [2] was handed to the American team which entered Hiroshima about a month later. The American group, which was commonly known as the Joint Commission, was composed of Navy, Army and Japanese personnel, and those from the Manhattan project. The Joint Commission completed their task by the beginning of 1946. Using the Japanese findings as a foundation, they expanded, confirmed and carried out further studies [1]. During the month of November, 1945, the Joint Commission was joined by a British Survey Team which evaluated the damage in the light of their experiences during the London "blitz" [5,10]. From January to November, 1946, there were no American investigating groups in Hiroshima as far as could be ascertained. In November, 1946, a small group known as the Brues-Henshaw Commission entered Hiroshima. This group had military as well as civilian personnel and took the name Atomic Bomb Casualty Commission (ABCC) [11]. In April, 1947, by act of Congress, the

Committee on Atomic Casualties was formed. This group took over the name Atomic Bomb Casualty Commission and it is this commission which is still carrying on investigations in Hiroshima.

MATERIALS AND METHODS

In 1949, ABCC conducted a census of all survivors of the atomic bomb in Hiroshima. This took six months to complete. One thousand fifty persons were found who had been exposed within 1,000 meters from the hypocenter. This group served as the basis for the adult Medical Program (ME-55) which was started in 1951. This program was composed of (1) all survivors exposed under the 1,000 meters and 10 per cent of the survivors exposed within 1,500 meters, totaling approximately 2,500 people, and (2) a control group consisting mainly of (*a*) people matched by sex and age with the exposed group, residing in the city of Kure (about 20 miles from Hiroshima) and (*b*) persons who moved into Hiroshima after January 1, 1946.

The Adult Medical Program started in 1951. All survivors on that program (and the few children on the pediatric program) exposed within 1,000 meters from the hypocenter were included in this study if they were still alive. There were 619 patients; 431 persons of the total 1,050 were lost due to death, refusal or inability to locate. Each case making up this paper was reviewed independently by each of us, and if there was any disagreement in a finding, we both reviewed the case.

Each patient was evaluated in two ways: (1) from the radiation symptoms and signs and (2) from the traumatic history. The radiation symptoms and signs were assigned numerical values as follows: vomiting, 1; fever, 2; oropharyngeal lesions, 4; purpura or petechia, 8; epilation of any degree, 16. Patients with any number or combination of numbers totaling between 8 through 31 were labeled severely radiated; from 4 to 7, moderately radiated; and from 1 through 3 lightly radiated. The basis for choosing the radiation symptoms enumerated were the chi square contingency tables between radiation symptoms worked out by Dr. L. Woodbury [*12*].

The evaluation of trauma was much more difficult. The effects of blast, burn and mechanical injuries were weighed by a doctor and patients were placed in one of the following three categories: (1) lightly injured, (2) moderately injured and (3) severely injured. These groupings were on a subjective basis. However, a patient so crippled by injury that he would have to depend on others for survival was classified in group 3. This group did not include persons temporarily unconscious who were able to care for themselves on recovery. Patients severely injured but capable of locomotion without aid were placed in group 2, e.g., punctured eyeball or fractured fibula. All patients with lesser type injuries were classed in group 1.

TABLE 1*
SEX AND AGE OF PATIENTS IN SAMPLE

Age at Time of Bombing (yr.)	Males	Females	Total
10–19	49 (17)	92 (27)	141 (23)
20–29	46 (16)	111 (33)	157 (25)
30–39	60 (21)	60 (18)	120 (19)
40–49	70 (25)	50 (15)	120 (19)
50–59	44 (16)	16 (5)	60 (10)
60 and over	12 (4)	9 (3)	21 (3)
Totals....	281 (45)	338 (55)	619 (100)

* All tables herein list both the absolute numbers of persons in various categories and the percentages in parentheses.

RESULTS

Trauma. There were 619 patients in the sample studied; 55 per cent were females and 45 per cent were males. (Table 1.) Most of the females were in their twenties, while the males were mainly in their forties. One might surmise that the numerous work parties in the city of Hiroshima would be composed of these age groups, as the females in their twenties are the most resilient and the strongest; the males in the third and fourth decades were in the Imperial Armed Forces. There were no children in the first decade in this sample. This has been explained by any one or a combination of the following factors [*13*]: "(1) A large mortality rate among children as a result of the bombing. (2) The evacuation of children from the cities prior to the bombing. (3) The inability to get exact information from young children."

The sample by exposure distance confirms the fact that there were more survivors the

TABLE II
SAMPLE BY EXPOSURE DISTANCE

Distance (meters from hypocenter)	Males	Females	Total
001–250	2 (0.7)	.....	2 (0.3)
251–500	14 (5.0)	17 (5.0)	31 (5.0)
501–750	47 (16.7)	57 (16.9)	104 (16.8)
751–1,000	218 (77.6)	264 (78.1)	482 (77.9)
Totals.....	281 (45)	338 (55)	619 (100)

TABLE III
DURATION OF HEALING

Type of Injury	Total Accumulative Per cent				
	25	50	75	90	95
Mechanical.....	2 wk.	4 wk.	11 wk.	20 wk.	24 wk.
Laceration.....	1 wk., 2 days	3 wk., 6 days	10 wk.	20 wk.	23 wk.
Flash burn.....	3 wk.	3 wk., 5 days	9 wk.	18 wk.	23 wk.

further the distance from the hypocenter. There were no differences due to sex. (Table II.)

In the number of injuries per person, excluding radiation injury, there was one person without any injury and ninty-seven people with abrasions. People with only one injury represented 60 per cent of the sample, 20 per cent had two injuries and 2 per cent had three injuries. Lacerations accounted for 80 per cent of all injuries, burns for 25 per cent and contusions for 15 per cent. It might be supposed that contusions should be the most common injury as undoubtedly most of the lacerations had a contused area.

In the group with two injuries, there were fifty-seven people with the combination of burns and lacerations, forty-five with contusions and lacerations, and twelve with burns and contusions. Of the twelve persons with the combination of three injuries, five had the combination of burns, contusions and lacerations.

The body was divided into five areas in locating injuries: (1) head, face, neck; (2) upper extremity; (3) thorax, back; (4) abdomen, pelvic girdle, genitalia; and (5) lower extremity.

Of the number of body areas injured, 221 persons had two areas injured and 226 persons had only one body area injured. Twenty-five people had injuries to all the body areas, ten to three body areas and thirty-four to four of the body areas.

During World War II, in the inter-war period, and during the Korean conflict, pleas were voiced [*14–16*] for the accurate location of wounds. Unfortunately the same chaotic conditions existing during combat were present following the bombing.

The head, face, neck area and the upper extremity area were the locations of the majority of the injuries. There appears to be a difference between the sexes as to number of injuries to the lower extremity ($P = 0.001$). The females with the higher percentage may have, in the privacy of their dwellings, shed their "mompei"* since it was early in the morning and during the heat of the summer. This would have removed a protective covering from flying glass and tile, and the flash.

The maximum duration of healing in mechanical injury ranged from less than one week to almost two years. (Table III.) In evaluating this type of injury for triage, the stockpiling of the equipment and the availability of beds, as to occurrence and duration the 25, 50, 75, 90, and 95 per cent levels were selected. Fifty per cent of the patients were completely healed by the fourth week following injury. By the twentieth week 90 per cent were healed, and four weeks later 95 per cent were healed.

Burns: There were twelve fire burns and 128 flash burns. The fire burns were contact burns; the flash burns were due to radiant heat transmitted in the visible and infrared regions of the spectrum [*17*]. The ultraviolet rays caused erythema but no burn. When an atomic bomb explodes, the flash is divided into two periods [*4*]. At first there is a short blue-white flash lasting about 0.01 second; this radiation does not persist long enough to ignite the surfaces on which it falls. This flash is followed by a longer flash which dies away relatively slowly [*2*]. Starting at about 20 to 25 milliseconds, skin burns are produced, with the most severe occurring between 0.1 and 0.2 second. By increasing increments of exposure, the major severity of thermal burns was attained within the first 0.3 second after the bomb exploded and the maximum severity within the first 0.5 second. No burns were produced after the first 0.6 second [*17*]. Therefore, protection from the

* Female work trousers demanded of all Japanese women during World War II.

TABLE IV
TYPE OF HEALING

Type of Healing	Flash Burns	Fire Burns	Lacerations
Primary intention	59 (46.8)	7	261 (53.7)
Keloid, with primary healing	1 (0.8)	0	0
Keloid, suppuration with delayed healing	5 (4.0)	0	0
Keloid, suppuration without delayed healing	7 (5.6)	0	0
No keloid, suppuration with delayed healing	17 (13.5)	2	152 (31.3)
No keloid, suppuration without delayed healing	35 (27.8)	3	73 (15.0)
No keloid, suppuration, non-healing	2 (1.6)	0	0
Totals	126	12	486

TABLE V
COMPLICATIONS OF HEALING

Complications	Males	Females	Total
Psychobiological	0	1	1
Cosmetic disfigurement	5	8	13
Physical incapacitation	10	9	19
Cosmetic disfigurement plus physical incapacitation	7	8	15
Totals	22 (45.8)	26 (54.2)	48

flash between 0.1 and 0.6 second after occurrence would result in no burn. Species differences and skin pigmentation also play a role in the severity of burns. Dark pigmentation at the same distance caused a more severe and more penetrating burn than light pigmentation; healing also took longer [17]. It is plausible to assume that the injuries due to flash burns may have been more severe because of skin pigmentation in our sample of Japanese people.

In 126 cases of flash burns (Table III), 50 per cent were healed by the fourth week, 90 per cent by the eighteenth week and 95 per cent by the twenty-third week.

The majority of the cases of flash burns healed by primary intention. About 10 per cent (thirteen cases) had keloids; in only one of the thirteen cases suppuration did not occur. Suppuration was present in sixty-six of the cases (52 per cent). (Table IV.)

Only twelve persons gave a history of fire burns. (Table IV). No keloids developed but there were several instances of suppuration.

Lacerations were the most common mechanical injury; 222 persons of 495 so injured gave a history of known duration of healing. (Table III.) Glass cuts represented 72 per cent of all lacerations. The 50 per cent level of healing was at four weeks, the 90 per cent level at twenty weeks, and the 95 per cent level at twenty-four weeks. The type of healing was recalled by 486 patients with lacerations. (Table IV.) Almost 50 per cent had suppuration of their wounds, although the majority healed by primary intention.

There were few skeletal injuries (total twenty-seven), and it is surmised that most patients with multiple fractures or a single incapacitating fracture perished in the "fire storms." Other fractures were undoubtedly missed because the patient never even suspected a fracture and it was only by x-ray examination that the diagnosis was made. Most of the fractures healed well with good alignment (fifteen of twenty-three). Only two patients had delayed healing. Six patients had poor alignment although the fracture healed well. The type of healing was unknown in four.

Forty-eight patients were found to have a complication resulting from healing. (Table V.) It is well known that many victims of any type of trauma always place the blame for any illness real or imaginary, on that event. Certainly the victims of the atomic bomb were not exceptions. However, the psychoneuroses and neuroses that may have resulted from that explosion were ignored in this study. The one patient listed as having a psychobiological complication was a schizophrenic. Whether she gave evidence of this condition prior to the bomb cannot be resolved. Twenty-eight patients suffered cosmetic disfigurement and it certainly can be assumed that there was some psychological overlay. The thirty-four cases of physical incapacitation were mainly due to contractures following burns.

Summarizing the severity of the trauma (Table VI), less than 1 per cent were very severely injured and about 93 per cent had mild traumatic injuries. Certainly this was to be expected, as the severely injured did not survive.

TABLE VI
DEGREE OF TRAUMA

Severity of Trauma	Males	Females	Total
None to mild	260 (92.6)	314 (93.0)	574 (92.7)
Moderately severe	20 (7.1)	23 (6.8)	43 (6.9)
Very severe	1 (0.4)	1 (0.3)	2 (0.3)
Totals	281	338	619

TABLE VII
SEVERITY OF RADIATION SYMPTOMS

Severity	Males	Females	Total
No symptoms	69 (24.6)	60 (17.8)	129 (20.8)
Mild symptoms	30 (10.7)	33 (9.8)	63 (10.2)
Moderate symptoms	0	0	0
Severe symptoms	182 (64.8)	245 (72.5)	427 (69.0)
Totals	281 (45.4)	338 (54.6)	619 (100)
Total number with symptoms and per cent of 619 patients	212 (75.4)	278 (82.2)	490 (79.2)
Per cent of 490 patients	212 (43.3)	278 (56.7)	490 (100)

TABLE VIII
ONSET OF RADIATION SIGNS AND SYMPTOMS

Symptom	Total Accumulative Per cent				
	25	50	75	90	95
Fever and/or vomiting	? hr.	? hr.	1 wk.	4 wk.	4 wk.
Oropharyngeal lesions	1½ wk.	3 wk.	3½ wk.	5 wk.	5 wk.
Purpura	1½ wk.	3 wk.	3½ wk.	5 wk.	6 wk.
Epilation	>1 wk.	2 wk.	4 wk.	6 wk.	8 wk.

TABLE IX
DURATION OF RADIATION SYMPTOMS

Symptom	Total Accumulative Per cent				
	25	50	75	90	95
Fever and/or vomiting	6 days	2 wk.	2 wk.	2 wk.	2 wk.
Oropharyngeal lesions	1 wk.	2 wk.	3½ wk.	6 wk.	8 wk.
Purpura	<1 wk.	2 wk.	3½ wk.	7 wk.	8 wk.

Blast: Blast injuries as such have not been mentioned. There were very few reports of such in Hiroshima and this quotation from the British Mission's Report [5] is a very appropriate one:

"In Nagasaki but not in Hiroshima, a rumor was current which age has made almost respectable, for it appeared in the London Blitz and before that in Barcelona during the Spanish Civil War. This was that large numbers of people had been ripped open by the blast, and their entrails exposed; their eyes and tongues were said to have hung out. Experience in this country (England) has shown that blast pressure alone does not in fact cause these sensational effects on the human body. It was, therefore, not unexpected that two Nagasaki survivors who had spoken of seeing hundreds or thousands of such bodies on examination reduced their claim to one or two. Flying debris would be expected to produce a few such injuries. Cases of genuine injury from high blast pressures, such as ruptured ear-drums, were rare among survivors."

Radiation Signs and Symptoms. As mentioned earlier, radiation injury was based on vomiting, fever, oropharyngeal lesions, purpura and epilation. There were 490 patients with symptoms, representing almost 80 per cent. (Table VII). The vast majority had severe radiation injuries with purpura and/or epilation, and perhaps other symptoms.

Fever and/or vomiting were the least significant symptoms of radiation injury, both biologically and statistically [12], and were evidenced by 74 per cent of the sample. (Table VIII.) The 50 per cent level of these symptoms occurred within hours of the detonation; these patients almost without exception had the symptom of vomiting. At the end of one week almost 75 per cent of this group had symptoms. The 90 and 95 per cent levels were reached in the fourth week. The duration at the 50 per cent level was two weeks and the main symptom was fever. (Table IX.)

Oropharyngeal lesions (Table VIII) were most difficult to evaluate from the history. The final criterion was ulceration of the oropharyngeal mucosa. Undoubtedly many cases did not meet this standard. When this type of lesion was present, the 50 per cent level was reached in the third week with the 90 and 95 per cent levels attained in the fifth week. The duration of this injury (Table IX) was comparatively short,

50 per cent being healed in two weeks and 95 per cent within eight weeks.

Purpura, which included petechiae and sponataneous bleeding from the gums, signified severe radiation injury. It was a manifestation startingly noticed by the layman, easily remembered and not influenced by the age of the patient. Over 50 per cent of the sample (Table VIII) had this symptom, with the 50 per cent level occurring in the third week, the 90 per cent level in the fifth week and the 95 per cent level in the sixth week. This sign lasted for two weeks (Table IX) for the 50 per cent level, and by nine weeks had disappeared for the 95 per cent level.

Epilation (Table VIII) was also a sign of severe radiation injury. It was startling and well remembered, but suffers as an indication of radiation because there appears to be a relationship with age [*12*], and also many men are bald-headed. The disappearance of epilation or reappearance of hair is not a good end point. The 50 per cent level occurred in the second week and the 95 per cent level in the eighth week. Although duration could not be evaluated, the degree of epilation was noted. (Table IX.) Over 60 per cent of the epilated patients lost almost their complete head of hair. Many patients remarked that their new growth of hair was at first finer and of a red tinge.

In trying to relate the traumatic injury to the radiation injury, it was believed that an inverse relationship might appear; the more severely traumatized the less severely radiated and, conversely, the less severely traumatized the more severely radiated. This was not borne out by analysis.

From these results one can hypothesize the modal patient in this sample study who survived at least five years after an atomic explosion and who was exposed within 1,000 meters. This patient was a twenty to twenty-nine year old female exposed between 750 and 1,000 meters from the atomic bomb. There was a 60 per cent chance of being lacerated and a 20 per cent chance of being burned. If an injury occurred it was most likely to the head-face-neck area or to an upper extremity. For any type of trauma the likelihood was that the injury healed by primary intention within four weeks. There was very little chance of any permanent complication of healing.

There was an 80 per cent chance of some radiation sign or symptom appearing. If there was fever and/or vomiting it probably started the first day (vomiting) and lasted two weeks (fever). If there were oropharyngeal lesions they appeared within three weeks and had a two-week duration. Purpura would be apparent within three weeks and would last three weeks. Epilation would begin within two weeks and would involve 76 to 100 per cent of the scalp.

This modal patient would experience severe radiation and mild trauma.

Several other studies similar to the present one have been made. It is of interest to compare the results. Table X lists the percentages of radiation, mechanical and thermal injuries found at different times by various investigators. These results were compared in the groups exposed through 1,000 meters. An excellent survey by Snell [*7*] could not be used, as his closest surviving group was exposed up to 1.0 mile. The Hatano survey [*6*] had a sample of 100 people, ninty-one of whom were exposed within 1,000 meters. Figuring that 10 per cent were exposed beyond 1,000 meters, this percentage was used to exclude the injuries that survey listed for the entire sample. As can be seen in Table X, the figures of the Joint Commission and this report are very similar. However, over-all there appears to be an increase in mechanical injuries and a decrease in thermal and radiation injuries. The increase in mechanical injuries could conceivably be due to the patients remembering injuries either occurred or imagined and not remembered five years previously, although this is very doubtful. The decrease in complaints due to thermal and radiation injury could be due to lapse of memory. There is another possibility which must be investigated: have the groups which were exposed within 1,000 meters with radiation and/or thermal injuries been dying at a faster rate than the groups with mechanical injuries or no injuries? In an effort to see if such a hypothesis could be advanced, all deaths of the exposed population within 1,000 meters on the ME-*55* program were collected. Of the original 1,050 contacts, fifty-four were dead. The various groups are listed in Table XI. The groups are so small that little can be said. There is an assumption that must be made: all patients flash-burned below 1,000 meters undoubtedly had some gamma radiation. At the present time the ABCC is making a detailed analysis of all deaths occurring in Hiroshima since the atomic explosion. It is from this

TABLE X

COMPARISON OF PERCENTAGES OF INJURIES FOUND AT DIFFERENT TIMES BY VARIOUS INVESTIGATORS

Type of Injury	J. I.* [2] Aug. 6, 1945	J. I. [2] and J. C.† [1] Aug. 8, 1945	J. C. [1] Sept. 1945	Hatano [6] Nov. 1945	ABCC‡ Jan. 1955
	Time Elapsed				
		% Dead before 20 days	% Alive after 20 days	% Alive after 104 days	% Alive after 5 yr.
Radiation	100	95.1	81.2	24.7	79.2
Severe radiation symptoms	...	58.5	75.2	....	69.0
Burns	90	57.2	25.1	16.0	24.4
Mechanical	...	57.2	61.8	71.8	88.7

* Japanese Investigation Group.
† Joint Commission.
‡ Present report.

TABLE XI

NUMBER OF DEATHS BY TYPE OF INJURY AND EXPOSURE DISTANCE

Injury	Distance (in meters) from Hypocenter				Total
	0–250	250–500	500–750	750–1000	
Burns	0	0	1 (33.3)	2 (66.7)	3
Radiation injury	1 (3.2)	2 (6.4)	2 (6.4)	26 (74)	31
Radiation injury and burns	0	0	1 (14.3)	6 (75.7)	7
Neither	0	1 (7.7)	3 (23.1)	9 (69.2)	13
Totals	1	3	7	43	54

analysis that the answer to the question posed previously will be found. One other attempt was made for a partial answer. The Metropolitan Life Insurance Company was asked about the death rates of survivors from the Texas City disaster, the Coconut Grove fire and severe automobile accidents. Their reply was that they had no information available and did not know of any group that might have such information. It would be of interest to know the effect of flash alone or with radiation injury on survival rates.

SUMMARY

Atomic bomb victims who were exposed under 1,000 meters and survived over five years were reinvestigated. There were 619 patients who comprised a total sample.

Mechanical, blast, burn and radiation injuries were evaluated as to onset, duration, severity, body area affected and type of healing. The modal patient experienced severe radiation and mild trauma.

Results were compared with similar earlier studies. The question emerges as to the possibility that patients exposed within 1,000 meters with radiation and/or thermal injuries have been dying at a faster rate than those with mechanical or no injuries.

A short history of the development of the Atomic Bomb Casualty Commission is included.

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One of every five babies born in the United States in 1910 died before reaching the age of 21. Today, the proportion is only one in twenty-five, according to the Metropolitan Life Insurance Company.

"Many forces have been at work to achieve these gains in health and longevity," says the Metropolitan's statistical bulletin. "Outstanding among the newer developments has been the introduction of the antibiotics, which have saved a great many lives among youngsters who in the past would have died from pneumonia, endocarditis, meningitis, and other infectious diseases."

Rebreathing Tube for Prophylaxis and Treatment of Atelectasis

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The prevalence and importance of pulmonary complications are well recognized today by both surgeons and anesthesiologists. While infection often plays an important role in the later course of a pulmonary complication, most of them start as atelectasis of some part or parts of the pulmonary tree. Various methods are in use to prevent the onset of atelectasis and to treat it when it does occur.

In the late 1940's the problem of postoperative atelectasis became increasingly apparent and was vigorously attacked by early ambulation, encouraging the patient to cough, the use of 5 per cent carbon dioxide administered by mask and early bronchoscopy for established lesions. Although this program of prophylaxis and treatment was used by increasing numbers of the staff and by 1950 it appeared that everything possible was being done, there was still an admittedly high incidence of postoperative pulmonary complications. It was decided to pursue this problem experimentally in the laboratory with the hope that if the basic physiopathology were understood more clearly, prevention and treatment might be easier. Studies were carried out on a large series of dogs in cooperation with Dr. Hermann Rahn of the Department of Physiology, and a more detailed understanding of certain aspects of the pathologic physiology of atelectasis was obtained [1–4].

During the course of these laboratory investigations of atelectasis some discussion of the effect of either decreasing or increasing the physiologic dead space of the respiratory pathway occurred and led to the idea that pulmonary ventilation could probably be increased at will if the patient's dead space were increased. Since it was assumed that one of the primary causes of atelectasis was failure of proper aeration in the postoperative, traumatized or unconscious patient, it was thought that such artificially induced hyperventilation might prove useful in the prophylaxis of pulmonary complications. In 1946 Otis, Rahn, Epstein and Fenn [5] had presented data from the Department of Physiology bearing indirectly on the problem of added dead space. Seven normal subjects were studied with four different added dead spaces for the effect on percentage of alveolar carbon dioxide, tidal volume and respiratory rate. Certain unpublished data obtained at that time were recalculated as indicated in Table 1. There was a gradual increase in percentage of alveolar carbon dioxide paralleling the added dead space. The tidal volume increased in a rather linear relation to the added dead space while the respiratory rate increased slightly but remained below 20 respirations per minute even with the largest volume of added dead space. This series of experiments were run with the patients breathing room air. Similar experiments were run on the same subjects breathing 100 per cent oxygen without much difference. Details of these experiments have been previously published [7], and the data are shown graphically in Figure 1 in which the results of breathing oxygen are shown to be quite similar to those of breathing room air. Figure 1 shows the almost linear relationship between ventilation and added dead space whether the subject breathes oxygen or room air. The original resting minute volume of respiration approximately doubled for each 500 cc. addition of dead space. The equivalent inspired carbon dioxide curve indicates that the addition of 1,000 cc. of added dead space is equivalent in its effect on ventilation to inhaling

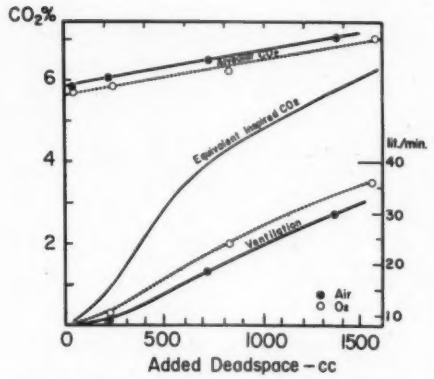

FIG. 1. Average data from six laboratory personnel breathing air (solid dots) and 100 per cent oxygen (open circles) through tubes of varied volumes.

approximately 5 per cent carbon dioxide. Further data from the study of subjects shown in Table I produced the graph in Figure 2, indicating that the increased ventilation was obtained at the expense of the inspiratory reserve while the expiratory reserve was essentially unchanged. In other words, the subject was stimulated by the increased alveolar carbon dioxide secondary to the added dead space to "reach out" beyond the added dead space and thus increase the tidal volume of respiration.

STUDIES ON NORMAL PERSONNEL

For clinical use it was recognized that a standard dead space tube would be necessary. Further studies similar to those aforementioned were made on nine laboratory personnel in order to select a proper volume for the dead space tube. Each individual lay supine with the head on a pillow, simulating a patient. After a nose clamp was applied the subject first breathed

TABLE I
SUMMARY OF DATA FROM SEVEN NORMAL SUBJECTS, MEASURED FIFTEEN MINUTES AFTER REBREATHING BEGAN

Calculated Added Dead Space (cc.)	Alveolar CO_2 (%)	Tidal Volume (cc.)	Respiratory Rate (per min.)	Minute Volume (L.)
35	5.8	635	13.2	8.4
225	6.1	715	12.6	9.0
720	6.5	1,120	16.7	18.7
1,360	7.1	1,680	18.1	30.4

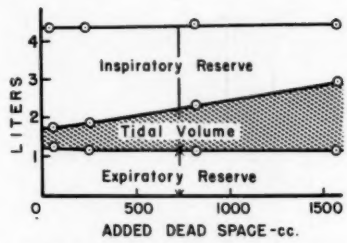

FIG. 2. Average effect of added dead space on tidal volume and reserves of six laboratory personnel.

through a rubber mouth piece and properly arranged one-way valves so that inspiration was from room air and expiration went through an electrically recording rapid flow gas meter so that minute volume, respiratory rate and tidal volume could be determined. Following a ten-minute control period, one of several rubber dead space tubes was inserted between the mouth piece and the valve and a ten-minute test run was made. After a considerable number of tests it was learned that a 1,000 cc. dead space tube with an internal diameter of 32 mm. and a length of 125 cm. resulted in the tidal volume of 1,364 cc.; this was an average increase of 770 cc. over the 594 cc. base line control tidal volume. In other words, the 1 L. dead space tube more than doubled the control tidal volume in laboratory personnel [7].

STUDIES ON PATIENTS

Fourteen patients undergoing varied surgical procedures were studied before and after surgery to learn the control tidal volume and the tidal volume stimulated by use of the 1,000 cc. dead space tube. Table II shows the average

TABLE II
AVERAGE TIDAL VOLUME OF FOURTEEN PATIENTS STUDIED PREOPERATIVELY AND DURING THE FIRST THREE DAYS AFTER OPERATION

Day	Control Rate (tidal vol. /cc.)	1,000 cc. Added Dead Space (tidal vol. /cc.)	Increase (%)
Preoperative.....	458	904	97
First postoperative...	401	922	130
Second postoperative.	410	925	126
Third postoperative..	416	942	127

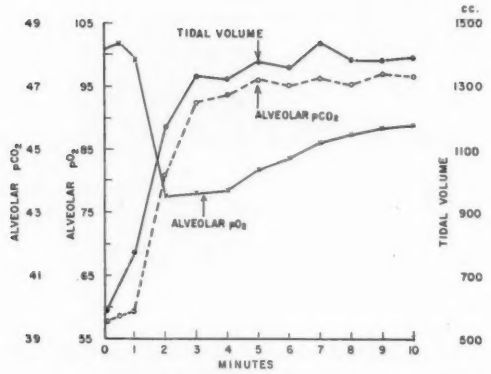

FIG. 3. Average data from fifteen normal patients breathing room air through 1,000 cc. dead space tube.

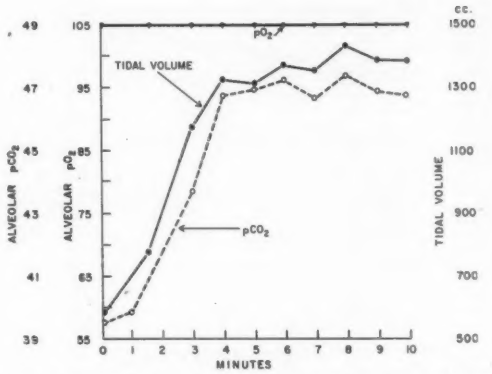

FIG. 4. Average data from three normal patients when 3 to 4 L./minute of 100 per cent O_2 was introduced into the distal end of the 1,000 cc. dead space tube.

data from these fourteen patients and indicates that while the 1,000 cc. tube caused a 97 per cent average increase prior to operation, it caused an approximately 126 to 130 per cent increase in the early postoperative period because the control tidal volume was somewhat smaller after surgery than it was before. There was no particular alteration of the respiratory rate. The reason for the failure of the stimulated tidal volume to be larger than the 1,000 cc. dead space was not completely clear but was possibly due to streaming of the gas through the tube so that the effective added dead space was less than actual tube volume.

Further studies were made to determine the relationship between the stimulated tidal volume, the alveolar carbon dioxide content, and the alveolar oxygen content on fifteen patients with normal pulmonary histories, physical examinations and x-ray findings. Figure 3 represents the average results of these clinical tests. The tidal volumes were measured by a rapid flow gas meter, and the alveolar sample obtained with a Rahn continuous alveolar air sampler [6] for a period of ten minutes during which time each subject breathed through the 1,000 cc. dead space tube. As Figure 3 indicates there was a steady increase in alveolar pCO_2 paralleling the tidal volume increase for about three minutes and becoming relatively stable thereafter. There was a decrease in alveolar pO_2 to approximately 77 mm. Hg at two minutes with an increase of some degree during the next few minutes. Whereas the decrease in alveolar pO_2 (in Figure 3 breathing room air) was clearly demonstrated, Figure 4 illustrates the results of the same study carried out with the patients breathing oxygen at a flow of 3 or 4 L. per minute into the end of the dead space tube. Here it may be noted that there was at no time a decrease in the alveolar oxygen tension. Comparison of Figures 3 and 4 indicates not only that the alveolar oxygen tension can be maintained by a low rate of oxygen flow into the end of the dead space tube, but also that oxygen is not the critical factor in determining the tidal volume and that the hyperventilation is basically due to the increased carbon dioxide tension of the blood acting on the brain.

CLINICAL USE OF TUBE

The experimental background appeared sufficiently encouraging to permit further clinical testing and a prototype (black rubber) dead space tube was, therefore, introduced on one general surgical floor. The tube was used for a period of several months under supervision of the floor personnel including both staff and private duty nurses. After approximately three months the use of this crude tube was extended to the entire Strong Memorial and Rochester Municipal Hospitals and has been in constant use until the development of a light cardboard tube* recently allowed replacement of the old rubber tubes. This new tube is pictured in Figure 5. It consists of a lightweight cardboard cylinder which slips inside a plastic mouthpiece. This lightweight device is placed between the lips, and the nose is closed either by the patient or by an attendant. The patient

* Obtainable from the Davol Rubber Co., Providence, Rhode Island.

FIG. 5. Clinical use of rebreathing tube, lips closed and nostrils pinched shut. Inset shows *incorrect* use of tube with mouth and nose open.

then breathes through the tube for a minimum of three minutes and a maximum of five minutes every two hours. Experience indicates that the newly developed cardboard tube with the plastic mouthpiece is considerably more acceptable than the laboratory prototype tube of rubber which was clumsy and which utilized a bad tasting rubber mouthpiece. The new tube allows sterilization of the mouthpiece in the autoclave. The cardboard tubes are discarded after use by a single patient.

Routine postoperative orders in these hospitals now include use of the tube every two hours for three to five minutes. While it is difficult to obtain exact figures on change in incidence of postoperative pulmonary complications, it is the impression of both the resident and attending staff as well as the nursing staff that there has been a decrease in the instance of pulmonary complications. Since the development of this tube, the use of paper bags and 5 per cent carbon dioxide inhalations by mask has been completely discontinued.

Patients occasionally object to the hyperventilation caused by the tube particularly if there is a thoracic or high abdominal incision. Preoperative explanation of the tube's purpose usually makes it easier for the patient to use the tube following operation.

SUMMARY

Hyperventilation with its attendant alveolar distention and stimulation of coughing is an important factor in the prevention and treatment of pulmonary atelectasis. A light cardboard tube of 1,000 cc. volume with a plastic mouthpiece has been developed, which by elevating the alveolar carbon dioxide tension stimulates such hyperventilation both in normal personnel and in patients before and after operation. Studies indicate the parallel changes in alveolar carbon dioxide tension and tidal volume which reach an equilibrium after approximately three minutes of rebreathing through the dead space tube. Some decrease in alveolar oxygen tension can be prevented by delivery of oxygen into the end of the rebreathing tube if necessary.

Routine use of this tube in patients postoperativly in the past year and a half has been useful in preventing and treating pulmonary complications. A regimen of three to five min-

utes rebreathing every two hours is recommended. Following each patient's use the cardboard tube is discarded and the plastic mouthpiece autoclaved prior to use by the next patient.

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If you grumble sometimes at what seems to be a high price tag on prescription drugs, you may be interested in some figures recently released by the national income division of the U. S. Department of Commerce. The proportionate cost of hospital care since 1929, for example, has almost doubled. Yet today we spend exactly the same percentage of our incomes for drug preparations and sundries as we did in 1929.

Vaginal Plastic Surgery Based on a New Concept of the Anatomy of the Female Genital Tract

VII. THE TECHNIC OF VAGINAL HYSTERECTOMY*

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DR. John H. Mulholland, in his Presidential Address before the American Surgical Association [1], made the following remark: "One cannot be taught, one must learn to be a surgeon."

These words of wisdom by a great teacher of surgery are particularly applicable to the younger surgeon who is ambitious to perform vaginal hysterectomies. He cannot depend upon being taught, but must learn how to do it. Therefore, it is not the purpose of this communication to attempt to teach anyone how to perform vaginal hysterectomy, but to point up certain basic principles in technic which I learned over the years.

In some clinics vaginal hysterectomy is a rare operation. Under such conditions, a resident, after having spent a number of years acquiring an abundant experience in abdominopelvic surgery, may not have had the opportunity to perform vaginal hysterectomy himself or may not even have seen his elders carry out such a procedure.

It is this type of surgeon I hope to reach—to encourage and to inspire him with confidence so that he may perform vaginal hysterectomy without fear or hesitancy whenever indications demand it, and not resort to the abdominal operation.

It is frequently argued that vaginal hysterectomy is a difficult operation to perform. It is not. However, assuming for the sake of argument that it is, should that be a deterrent when there is a definite indication for it? More difficult operations are performed in many clinics daily when they are thought to be to the advantage of the patient. Again, difficult is a relative term, and what may appear difficult to the beginner is eliminated by increasing experience.

It is also argued that there is excessive bleeding in vaginal hysterectomy, but there should not be. It will be shown herein (under "Operative Technic") that with proper precautions there may be less loss of blood than in a complete abdominal hysterectomy.

A motion picture demonstration of vaginal hysterectomy may give one the impression that there is much bleeding but actually it is more apparent than real. Working in a limited, narrow and confined space, as the surgeon does in this area, the little ooze may appear as a profuse hemorrhage which, of course, it is not.

Another objection offered is that there is so much danger of injuring neighboring organs such as the urinary bladder, the ureters or the rectum. Actually, injuries to these organs have occurred in abdominal hysterectomies. Their avoidance is simply a matter of good surgical technic and sound judgment, as must be exercized in any type of major surgery. The technic to be described will obviate such accidents.

One more objection occasionally voiced by antagonists is that vaginal hysterectomy is a long, tedious and time-consuming operation. This hardly deserves consideration and cannot be tolerated or condoned. The patient's welfare is more important than the convenience of the

* Parts I, II, III, IV, V and VI appeared in the May, July and October 1957 issues, and the March, May and July 1958 issues, respectively, of *The Americal Journal of Surgery*.

surgeon. It does not take any longer to perform vaginal hysterectomy than a complete abdominal hysterectomy, if we take into account the time spent in opening and closing the abdomen.

It might be of interest to compare the advantages of a vaginal hysterectomy over the abdominal operation: (1) There is practically no shock after vaginal hysterectomy. It is gratifying to see the patient a few hours after the operation and find her promptly reacted, quite alert and comfortable, with a normal pulse, respiration and temperature. (2) There is almost no nausea or vomiting postoperatively. The Levin tube has no part in the postoperative treatment. (3) The operation can be performed under local anesthesia. This advantage in feeble, elderly and what generally might be considered poor-risk patients can hardly be overestimated. (4) Most significantly, the cervix is removed in every case in vaginal hysterectomy. It is hardly necessary to stress the importance of this.

THE OPERATIVE TECHNIC OF VAGINAL HYSTERECTOMY

The technic to be described takes full cognizance of all the unfavorable elements cited, and every effort is made to counteract or eliminate them. Each step of the operation will be described in considerable detail, to convey to the surgeon so perfect a mental concept of the operation as to enable him to perform it with ease and confidence, and to help him anticipate and avoid the pitfalls so frequently attributed to this valuable and most interesting surgical procedure.

Adhering to those principles, the operative procedure will be described as consisting of three parts: (1) The preparatory stage, directed toward the approach and exposure of the uterus. (2) The technic of the removal of the uterus, the actual hysterectomy. (3) The final stage of the operation to which a great deal of attention will be devoted. It will be pointed out later how this will help prevent and eliminate the complications and sequelae so frequently attributed to vaginal hysterectomy.

Part 1

It should be stated at the outset that the services of a competent assistant play a very important part in performing vaginal hysterectomy. In fact, one should not attempt this operation unless he has provided himself with a competent first assistant. The second assistant, whose function is limited mostly to the holding of retractors, may be of considerable help during the progress of the operation. With the team thus organized, the operation is begun.

The Opening of the Cul-de-sacs. The best way to approach and expose the uterus is by opening both the anterior and posterior cul-de-sacs; it is better to start with the posterior cul-de-sac because most of the bleeding so frequently complained of comes from this part of the vaginal wall, and it is so much easier to prevent and control such bleeding during the early part of the operation. However, it will be shown presently how such bleeding can be prevented entirely.

The opening of the posterior cul-de-sac: The cervix is grasped with a Jacobs clamp and is pulled up toward the arch of the pubis, exposing the rim of the cervicovaginal junction. At this stage a certain measure is utilized which will prevent the possibility of any excessive bleeding in this area: a chain stitch catgut suture is used through the vaginal wall about 1 cm. from its junction with the cervix and is applied to the posterior half of the circumference of the vaginal rim. This suture controls both the efferent and afferent vessels.

An incision is made close to the cervix (and parallel with the suture) through the mucosa-muscularis of the vaginal wall. If an occasional bleeder makes its appearance, it is promptly clamped and ligated. There must be no bleeding.

The muscularis is stripped back for about 1 cm. and the connective tissue coat of the vaginal wall (or pelvic fascia) is exposed. It is incised to the same extent as the primary incision, and the pelvic peritoneum becomes visible. The peritoneum is picked up with two Kelly clamps, incised to the full extent of the previous incision and the cul-de-sac is entered. The opening may be enlarged by inserting a finger in each angle of the wound and stretching it

At this stage the pelvis may be explored digitally, if necessary. A little more traction on the cervix brings the sacrouterine ligaments into view. Each ligament is double-clamped near its junction with the uterus, and cut between. A transfixion suture is tied on the proximal end of each ligament; the ends of the suture are left long and are allowed to hang, clamped, over the draping.

The clamps on the distal ends of the ligaments are then removed. As a rule there is no bleeding from those ends, but if there is they should be promptly clamped and ligated.

If loops of small intestine appear in the

wound, the table is promptly placed in the Trendelenburg position and a small pack of gauze is inserted through the opening in the cul-de-sac. A clamp is applied to the lower end of the gauze to prevent its disappearance into the peritoneal cavity.

The opening of the anterior cul-de-sac: This part of the operation is almost an every day practice in gynecological clinics, but in the case of vaginal hysterectomy two elements require special attention: (1) The "usual bleeding" cannot be regarded with equanimity. Bleeding obscures the operative field and normal landmarks, and may inadvertently be the cause of an injury to a neighboring organ. (2) There is the additional element of opening the peritoneum which must always be done with a certain amount of care and caution.

To open the anterior cul-de-sac, traction is made downward on the cervix, and the anterior vaginal wall is straightened out. The usual longitudinal incision is made as is customary in the so-called cystocele operation, but first only through the mucosa. Every bleeding point is caught and ligated. The circular layer of the vaginal muscularis is now exposed. This is incised with short snips of the scalpel, a spreading of the lips of the wound will be observed and the longitudinal fibers of the muscularis become exposed in the depth of the wound. The circular layer is quite vascular and every bleeder must be promptly taken care of.

The longitudinal fibers must not be cut; they are split in the median line by use of the blunt end of the scalpel, gently retracted to either side and separated from the underlying bladder with extreme gentleness and care. If there is any bleeding from either surface, clamps should not be used, the bleeding is controlled by the use of Atraumatic® sutures.

With the bladder now fully exposed and completely separated from the vaginal wall, the frenum-like vesicouterine ligament is picked up with a thumb forceps and cut. The bladder is separated from the uterus by gentle, blunt dissection until the triangular tongue of the peritoneum appears in the upper part of the wound. There is usually no bleeding in this area but if an occasional vessel is encountered it must be promptly clamped and ligated. As was urged previously, there must be no bleeding.

A small vaginal pack is placed against the bladder and is held in that position temporarily with a small retractor by the second assistant.

The lateral vaginal flaps are now cut away from the cervix. Bleeding from the cut surfaces may be easily prevented by the use of a preliminary chain stitch suture on the lower part of each flap (as was done on the posterior vaginal rim) or the cut margin of each flap may be clamped as a bleeder appears.

The peritoneum is picked up with two Kelly clamps and cut between for about 2 cm. and no more. A black silk suture is now passed through the upper flap and tied. The ends are left long, carried above the pubis, and sutured or clamped to the draping. This is very important. If this precaution is not taken it may be quite difficult to find the flaps at the end of the operation and it would be impossible to close the peritoneum, which is an essential part of the technic to be described.

The opening in the peritoneum is now extended to the broad ligament on each side. The fundus of the uterus is palpated to determine its position in the pelvis and its size. This is of importance regarding its delivery, as shall be noted later on.

It will be observed that the uterus and the cervix have been completely freed from their attachments, except for the broad ligaments on either side. (The proximal end of the round ligaments and also of the fallopian tubes are practically an integral part of the top of broad ligaments.) The broad ligaments, in turn, have also been exposed and have been made accessible by the openings in both cul-de-sacs.

Part 2

This part of the operation, as has been indicated, consists of the excision of the uterus but, essentially, it is accomplished by section of the broad ligaments on each side; the uterus then just drops out. Therefore, all attention is now concentrated on the broad ligaments.

Section of the Broad Ligaments. There are three methods of approaching the broad ligaments and starting their section: (1) The fundus of the uterus is brought forward through the opening in the anterior cul-de-sac. (2) The process is reversed and the fundus is brought out through the opening in the posterior cul-de-sac. (3) The uterus is not disturbed at all. It remains *in situ*, but section of the broad ligaments starts below, at the bases, and is continued from below upward toward the top of each.

There are definite indications for the application of each of the several methods. The choice is determined by certain factors: the size of the

uterus, the position of the uterus in the pelvis, and occasionally by the angle of the arch of the pubis.

If the uterus is of moderate size, its position is high in the pelvis and it is about normally anteflexed, it is readily accessible; then the first method is naturally to be used.

If the uterus is still of about moderate size and placed low in the pelvis, as in cases of prolapse or even moderate descensus, or in marked retroversion, the second method is definitely indicated.

If the uterus is rather large and the surgeon with sufficient experience believes that it can be removed by the vaginal route, the third method facilitates the procedure, as will be described later.

It may be put down as a general rule that if the uterus can pass through the pelvic outlet, it can be subjected to vaginal hysterectomy. However, if the arch of the pubis forms an acute angle, it would be difficult to carry out the procedure to be described.

First method: The bladder should be catheterized before any attempt is made to deliver the fundus of the uterus.

The cervix, still held with the Jacobs clamp, is now brought down and pushed back toward the sacrum as far as possible. That will bring the fundus closer to the opening in the anterior cul-de-sac. One or two fingers of the left hand passed through the opening steadies the fundus and a hook or another Jacobs clamp grasps the fundus, which is then gradually and slowly coaxed through the opening. Haste and force are to be avoided, as needless trauma may be caused.

With the fundus out, section of the broad ligament is started. The left broad ligament is double-clamped close to the uterus for about 2 cm. That includes the proximal ends of the round ligament and of the fallopian tube on that side. The broad ligament is cut between the clamps with the scalpel, and the proximal end is transfixed with a suture ligature.

A bite is now taken, with the same suture, through the round ligament and tied. If this is not done, the suture may slip off and become loose; this has happened in my experience.

The ends of the suture, left long and loose, are carried above the pubis and are clamped to the draping close to the silk suture mentioned previously. This suture should not be held by a human hand, as it may be inadvertently pulled out and followed by a distressing hemorrhage.

The right broad ligament is now double-clamped, cut and sutured in exactly the same manner as was done on the left side. The ends of the suture are carried above the pubis and clamped to the draping.

From here on small sections of each broad ligament, about 1 cm. in extent, are clamped and cut and transfixed with suture ligatures, but the ends are cut short. This is continued first on one side of each broad ligament and then on the other, until the base of each broad ligament is reached. When the last suture is completed, the uterus is free and is lifted out and removed.

Each stump of the broad ligament is carefully inspected, and if there is the slightest evidence of any bleeding, this part should be resutured. One must never depend upon ligation in this area.

Second method: Traction is made on the cervix in the opposite direction, that is, toward the pubis. This brings the fundus of the uterus closer to the opening in the posterior cul-de-sac. Here, too, guided by a finger or two in the cul-de-sac, the fundus of the uterus is brought down toward the opening and is grasped by a hook or a Jacobs clamp.

Section of the broad ligament is carried out in the same manner as described under the first method, except that we proceed from below upward. The first transfixion suture takes an additional bite in the round ligament, for the same reason as indicated previously. The ends of these sutures are left long and are allowed to hang down over the draping near the sutures on the sacrouterine ligaments.

Section of the rest of each broad ligament is continued in the same manner practiced in the first method. Small bites are taken, about 1 cm. in extent, transfixed with suture ligature, and the ends are cut short. When section of both broad ligaments has been completed, the uterus is free and is lifted out of the wound. The cut surface of both broad ligaments is examined for any possible bleeder and, if one is found, it is promptly suture ligated.

Third method: As has been stated previously, the large uterus is not mobilized but is kept in its natural position. The vaginal cuff, it is assumed, has been completely freed from around the cervix so that the base of each broad ligament is freely exposed.

Section of each broad ligament is started at the base and is continued upward. The base of each broad ligament is double-clamped as close

to the uterus as possible, cut between, and the proximal stump is transfixed with a suture ligature. The ends are cut short.

Section of the broad ligaments is thus continued upward to within 2 or 3 cm. of the top. It will be observed that the uterus has by this time dropped down considerably.

The cervix is swung over to the right, revealing the top of the left broad ligament. It is double-clamped close to the cornu of the uterus, cut between, and the stump is transfixed with a suture ligature. The ends of the suture are left long and allowed to hang down over the drapes. The top of the right broad ligament is treated in the same manner. The uterus is now free and is lifted out of the wound. Here, too, as previously indicated, the margin of the cut surface of each broad ligament is examined for any possible bleeder and, if found, it must be suture ligated. It cannot be repeated too often that there must be no bleeding.

This completes the second part of the vaginal hysterectomy. As we are now approaching the third part of this operation, it is essential to point out that the technic to be described is not limited to just "closing the hole" created by the operation but has an entirely different and more important implication.

The technic is directed toward the restoration of normal anatomic relationships and the reconstruction of a vaginal vault which will not only provide good support for the superjacent structures but also serve to prevent the unfortunate complications and sequelae that have plagued surgeons for a long time. These include the postoperative formation of an "enterocele," the prolapse of an ovary or a fallopian tube, a short or shallow vagina, or even complete inversion of the entire vaginal tube. On occasions, a loop of intestine has escaped through the unclosed peritoneum and become strangulated.

Part 3

With the uterus out, the following conditions exist: the pelvic peritoneum is still open, the vault of the vagina is minus the cervix, and the wounds of the anterior end of the posterior vaginal walls are open.

In addition, there are clamps and sutures on certain important structures: two clamps on the stumps of the broad ligaments, one clamp on the silk suture on the bladder flap of the peritoneum, and two clamps on the sacrouterine ligaments.

The Reattachment of the Sacrouterine Ligaments. Each ligament is sutured to the lower flap of the peritoneum, that is, the one lining the upper part of the posterior vaginal wall. Each ligament is transfixed with a silk suture and a deep bite is taken into the peritoneal flap and the vaginal muscularis, but not the vaginal mucosa. However, the attachment of the sacrouterine ligaments in this manner will serve an important function in the formation of a high vaginal vault.

The Closure of the Peritoneum. This is not usually practiced, judging by the descriptions and illustrations in textbooks. However, it is very important in the final steps of the operation and its omission cannot be regarded lightly. Ignoring it exposes the patient to the danger of the complications and sequelae already referred to.

The operative technic: At this stage the bladder must be catheterized, for if it is distended with urine it is practically impossible to bring the flap down.

With the bladder emptied, traction is made on the silk suture on the bladder flap of the peritoneum and the latter comes readily into full view. The lower flap of the peritoneum (the one lining the posterior vaginal wall) is brought up and the two flaps are joined together in the center by a chromic suture which is tied but not cut. The silk suture is removed.

The rest of the opening in the peritoneum is closed with a few interrupted, chromic, mattress sutures to each side of the primary (the central) suture, up to the ovarian ligaments on each side. In that way the ovaries remain within the peritoneal cavity and are not likely to become prolapsed through a faultily constructed vaginal vault. The stump of the upper parts of the broad ligaments are left outside or beneath the peritoneal cavity and will now be taken care of.

Gentle traction is made on each suture on the stump of each broad ligament, and the stumps are held together in the center of the wound. The central suture is now passed through both round ligaments, and is tied but not cut. If the broad ligaments have considerable thickness, an additional bite may be taken through them with the same central suture. If they are not of sufficient bulk, this must be omitted as a laceration may occur and bleeding start.

The posterior vaginal wall is now brought up against the broad ligaments, and a deep bite is taken with the needle of the same central suture

through the vaginal muscularis, and tied. (The mucosa must not be included.)

In this part of the operation the following has been accomplished: the pelvic peritoneum is closed tight; the ovary remains within the peritoneal cavity; the broad ligaments have been placed under the peritoneum, as is done in abdominal hysterectomy (this holds up and provides a certain amount of support for the peritoneum); and a good cul-de-sac of Douglas has been established.

In addition, a very important element has been added. By suturing the posterior vaginal wall to the broad ligaments and attaching the sacrouterine ligaments to this part of the posterior vaginal wall, bulk is added to what will presently become the new vault of the vagina and the upward pull of the sacrouterine ligaments results in a high vaginal vault. This will eliminate the possibility of a short or shallow vagina. Then, with the fusion and union of these several elements, a prolapse or inversion of the vaginal tube is not likely to occur.

The longitudinal incision in the anterior vaginal wall is closed by a number of interrupted, submucous, mattress sutures. This results in an open, transversely placed wound, separating the margin of the anterior vaginal wall from that of the posterior. These are now brought together in a similar manner by interrupted, chromic sutures. The reconstruction of the vault of the vagina is now complete.

A correspondent has asked how to prevent the resulting short vagina when vaginal hysterectomy is performed for prolapse of the uterus. As a matter of fact, this is responsible for the prevailing idea among some gynecologists that vaginal hysterectomy does not cure prolapse.

It must be realized that in cases of prolapse another element must be taken care of in addition to removal of the uterus. In the development of the prolapse, as the uterus begins to sink in the pelvis it drops down and stretches the sacrouterine ligaments, pulling down at the same time some adjacent peritoneum. If this were viewed from within the abdomen, it would appear as a hernial sac and a deep cul-de-sac of Douglas. Actually, it is neither. It is not the cul-de-sac at all because neither the uterus nor this part of the vagina are ever in direct relationship with the pelvic floor, and it is not a true hernial sac because it is only a part of the peritoneum that is pulled down with the posterior vaginal wall.

Therefore, after removal of the uterus, a part of the peritoneum is stripped off the posterior vaginal wall and is excised, the sacrouterine ligaments are attached to it and the remaining flap is brought up to the bladder flap of the peritoneum to be sutured. This eliminates the so-called "enterocele." Also, as the stumps of the broad ligament are sutured under the peritoneum and the posterior vaginal wall is sutured to the broad ligaments, as described, a high vault of the vagina will be constructed and a long vagina will be the result.

The omission of the mucosa in the closure of these wounds has been stressed quite frequently and there is very good reason for that. It is based on the principle that the surface of the mucosa is never free of bacteria. If the mucosa is included in the closure, every stitch hole provides a passageway for infectious agents to enter the deeper tissue from tiny abscesses, perhaps only microscopic in size, which will cause malodorous drainage and even a complete breakdown of the wound.

However, if good coaptation of the wound is accomplished by the submucous sutures, there is no need to include the mucosa. Mucosal wounds heal very rapidly, practically overnight, if the edges of the wound are properly approximated.

The bladder is catheterized once more. This has a double purpose: first, to make certain that there has been no injury to the bladder, which would be manifested by some blood in the urine and, second, that the patient will not be disturbed for early catheterization by the overanxious nursing staff.

A small piece of iodoform gauze is left in the vagina to absorb moisture. It is removed in twenty-four or forty-eight hours.

POSTOPERATIVE TREATMENT

As a general rule, patients who have undergone hysterectomy require very little postoperative care. They receive some sedation the first twenty-four hours, but never to the extent required after abdominal hysterectomies.

In most cases, if the bladder has not been unduly traumatized, the patient will void spontaneously. However, to avoid any possible retention and overdistention of the bladder, it may be advisable to catheterize the patient occasionally to eliminate those possibilities.

CONCLUSION

It is my sincere hope that the simplified technic of vaginal hysterectomy described in this article will be of help to those surgeons who have experienced difficulties in performing this operation.

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The Clinical Evaluation of a New Anti-inflammatory Agent

A PRELIMINARY REPORT

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IN the past four to five years the acceptance of the host's local reaction to injury known as inflammation has received a number of critical challenges [1–6]. These challenges have been directed at the advantages available if the usual local inflammatory reaction can be modified; thus erythema, edema and local cellular infiltration may be eliminated or markedly decreased without prolonging or complicating wound healing.

In a previous report we evaluated five anti-inflammatory agents, namely, streptokinase, trypsin, cortisone, Hydrocortone® and phenylbutazone [7]. Of this group, oral phenylbutazone was the most effective and least toxic for this short term ancillary therapy in surgical lesions.

During the past year we have expanded our studies to include a metabolic derivative of phenylbutazone known at present as G-27202.*

This work was carried out in the Surgical Research Laboratory and on the wards of St. Vincent's Hospital of the City of New York.

MATERIALS AND METHODS

G-27202 is a para hydroxy derivative of phenylbutazone which appears as a metabolite in the urine of patients receiving the parent drug.

The substance is readily soluble in alkaline aqueous solution. Its acute toxicity is similar to phenylbutazone. Chronic toxicity, especially gastrointestinal ulceration and hemorrhage, appears to be markedly less than the parent drug. After intravenous injection in man, G-27202 disappears from the plasma at a rate indicating a half-life of two to three days.

Dosage schedules have been arbitrarily selected at present. In this series a priming dose of 300 mg. followed by a 100 mg. dose every six to eight hours for two to three days has been employed.

In all patients suspected of having a bacterial focus associated with the inflammatory reaction, a parenteral antibiotic has been concomitantly given.

In this study some forty-eight patients have been given courses of therapy with G-27202. In all, fifty-five courses of therapy have been carefully screened. The patients had lesions ranging from acute cellulitis to clean surgical incisions. All forms of muscle strain, ligament tears and arthritic changes were studied. In a number of instances these patients had not responded to short courses of salicylates and narcotics.

RESULTS

The results obtained in this preliminary study are demonstrated in groupings of similar inflammatory reactions. (Table 1.) As this study was primarily designed for surgical lesions, only one patient with degenerative osteoarthritis was studied. In most instances the lesions were of recent origin except those listed under edema. Treatment on the average was concluded within forty-eight to seventy-two hours on the aforementioned arbitrarily selected dosage level. The term *excellent* was utilized to describe that result of therapy in which the various signs of inflammation subsided in six to twenty-four hours. *Good* was employed if modifications in the inflammatory process were noted in twenty-four hours but when forty-eight to seventy-two hours of

* G-27202 furnished by Geigy Pharmaceuticals, Ardsley, New York.

TABLE I

COMPOSITE RESULTS IN FIFTY-FIVE PATIENTS GIVEN G-27202

Type of Illness	No. of Patients	Duration of Symptoms (average)	Dosage (average)	Duration of Treatment (average)	Toxicity	Results of Therapy			
						Excellent	Good	Fair	Poor
Arthritis, degenerative	1	2–3 yr.	300 mg.	2 days	0	0	1	0	0
Arthritis, post-traumatic	12	2–3 days	300 mg.	2 days	0	12	0	0	0
Bursitis and tendinitis	3	24 hr.	300 mg.	2 days	0	2	1	0	0
Myositis, acute	7	48 hr.	300 mg.	2 days	0	7	0	0	0
Acute trauma: Contusions and sprains	9	12–36 hr.	300 mg.	2 days	0	8	0	1	0
Infections: Ulcerations and abscesses	7	24–72 hr.	300 mg.	2 days	0	6	0	1	0
Edema	5	48 hr.–10 days	300 mg.	2–3 days	0	4	1	0	0
Peripheral neuritis	5	48 hr.	300 mg.	2–3 days	0	3	2	0	0
Postoperative pain control	6	.....	400 mg.	4 days	0	6	0	0	0
Totals	55	.....	.....	.....	0	48	5	2	0

therapy were required for control. Those lesions listed under *fair* were modified over a seventy-two–hour course of therapy but complete clinical control was not obtained. In no instance was a poor result obtained.

COMMENTS

As a full detailed report will be forthcoming when a larger series is available, we would like to point out some of our more interesting findings. We have noted that in most postoperative states the patient's chief complaint of wound pain occurred some four to sixteen hours after surgery. The underlying basis for pain in the first hours may be due to trauma from stretching of muscles by retractors or other manual manipulations. It is our premise that this pain developing in the eight to sixteenth hour postoperatively was due to an inflammatory reaction secondary to operative trauma.

A group of patients undergoing hemorrhoidectomies, skin grafting, skin incisions with the excision of deep lying bronchogenic cysts and abdominal exploration were given a priming dosage of 300 mg. of G-27202 eighteen hours before surgery and one 100 mg. capsule ten hours prior to surgery. After the operation and when the patient could tolerate fluids by mouth, the routine dosage of 100 mg. every eight hours for forty-eight hours was given. In each instance postoperative pain was reduced to slight discomfort, and no narcotics or antibiotics were given. In no instance has wound healing been delayed. A full scale study of these findings is now under way.

We have noted that in the acute myositis, bursitis, tendinitis and trauma groups response to G-27202 has been more rapid than that experienced in the study employing phenylbutazone.

In those patients with edema, secondary to inflammatory disease, the subsidence time is about the same as occurred with the parent drug.

TOXICITY

In only one instance did a patient with acute trauma regurgitate the capsules shortly after ingestion. In fact, the capsules were still intact. No other gastrointestinal reactions have been noted. Three patients undergoing this short course of therapy had known but healed duodenal ulcers and to date have had no recurrence following therapy.

Toxicity studies included complete blood counts, multiple urinalyses, determinations of blood urea nitrogen, prothrombin time, thymol turbidity and alkaline phosphatase levels, as

well as clinical evaluation of pulse, temperature and frequent blood pressures. In no instances were alterations noted due to employment of G-27202.

SUMMARY

1. G-27202, a metabolic derivative of phenylbutazone, has potent anti-inflammatory properties.

2. This agent has not demonstrated any toxic effects during short term therapy on the dosage schedule outlined.

3. The use of anti-inflammatory agents may play a definite ancillary role in reducing inflammation due to surgical intervention.

4. Further studies on the basic activity of this agent in the role of a host modifier in clinical trials are in progress.

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Although studies by some insurance companies have shown overweight to be more common in women, recent studies by the Public Health Service indicate that overweight occurs nearly twice as frequently among men in the white population, according to the current issue of *Patterns of Disease*, published by Parke, Davis & Company for the medical profession.

Among non-white persons, obesity (a condition defined as one in which weight is 20 per cent or more above normal) is more prevalent among women. Incidence of overweight is believed to have declined among women and increased among men in recent years.

Bilateral Ligation of the Hypogastric Arteries

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Elective ligation of the right and left hypogastric arteries (internal iliac arteries) was first proposed in 1893 [1] as a technical procedure and essential preliminary step to radical surgery in the pelvis. Bilateral ligation was included in operations performed by Dennis [2] and Meyer [3] in the United States, by Makins [4] and Treves [5] in England and by Baudet and Kendirdjy [6] in France. However this procedure was soon abandoned because of the high mortality rate and the uncertainty of the end effects of the vascular occlusion. It seemed then that ligation of both hypogastric arteries threatened the viability of intrapelvic viscera and was causative of regional necrosis in the perineum. The return to exenteration for advanced carcinoma in this region has again revived the problems associated with ligation of both major vessels in the pelvis. Anatomical, experimental and clinical studies have been made to evaluate this technique.

SURGICAL ANATOMY

A total of 150 student and graduate dissections of the hypogastric artery and its branches were examined in the anatomy laboratory of the New York University College of Medicine. Each artery, right or left, was classified according to one of five type variations as described by Lipschutz [7] and with some modifications have been illustrated in Figure 1A to E. Significant measurements of vessel length, relationships to fixed anatomical points of reference and to neighboring structures were compiled and summarized in Tables I and II. The collateral circulation and the cross circulation over the midline were determined by intra-arterial injection of red lead suspension with only one and with both hypogastric arteries occluded at their origin. (Figs. 2 and 3.)

Anatomists and surgeons have noted the frequency in the variations of the hypogastric artery and its branches which have been broadly classified as embryologic anomalies due to defective arteriogenesis. More critical study has shown that these unclassified variations could be grouped on a morphogenetic basis according to the five characteristic patterns as indicated in Figure 1A to E. Examples of the variations of several surgically important branches have been outlined in Table III. Their identification *in vivo* could be accomplished only by an extensive dissection deep in the hollow of the pelvis. Surgical control of these vessels is both difficult and dangerous if approached locally, especially in the presence of diffuse pathologic conditions. Permanent or temporary occlusion of the hypogastric arteries is the safer procedure which reduces the hazards of excisional surgery in this region.

An outline of the iliac arterial system may be projected on the abdominal surface by the following guide lines. The first begins from a point ½ inch below and to the left of the umbilicus and extends directly to the midpoint of a line which connects the anterior superior spine of the ilium with the symphysis pubis. The upper third of this umbilicospinal line marks the course of the common iliac artery. The distal two-thirds corresponds to the course of the external iliac artery. From the latter junction point and at an acute angle of less than 80 degrees, a short line directed toward the pelvic floor in a medial direction indicates the line of the hypogastric artery. The site of emergence of the hypogastric artery from the pelvis is located on the line from the anterior superior to the posterior superior spine of the ilium at its proximal third.

The hypogastric artery (Fig. 4) arises from

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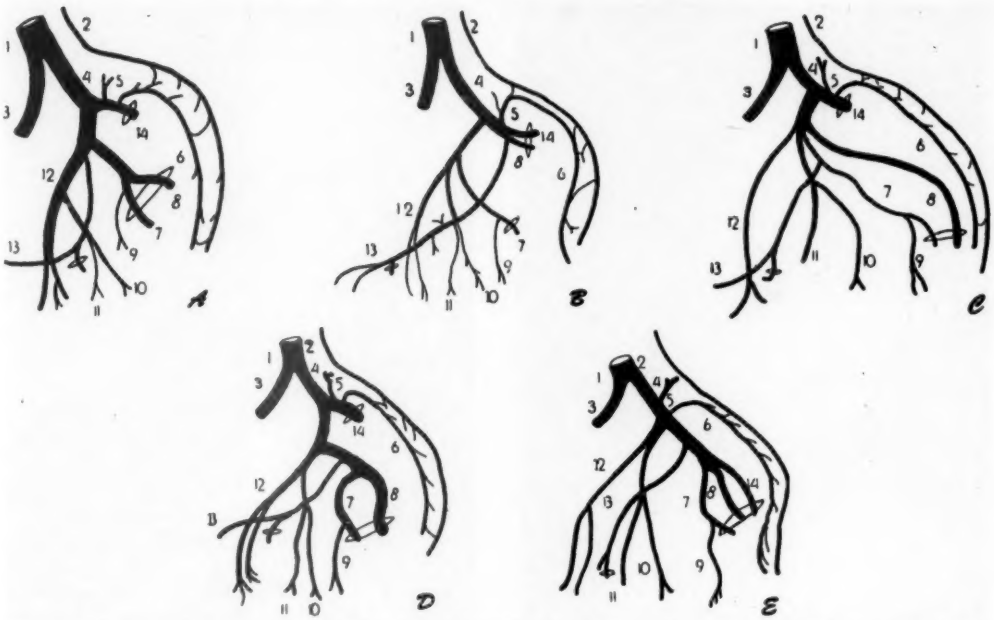

KEY: (1) Common iliac artery; (2) middle sacral artery; (3) external iliac artery; (4) internal iliac artery; (5) iliolumbar artery; (6) lateral sacral artery; (7) internal pudendal artery; (8) inferior gluteal artery; (9) middle hemorrhoidal artery; (10) inferior vesical artery; (11) uterine or deferential artery; (12) umbilical artery; (13) obturator artery; and (14) superior gluteal artery.

FIG. 1. Variations of the branches of the hypogastric artery.

A, type I (incidence, 36 per cent). The superior gluteal artery constitutes the posterior trunk. The inferior gluteal artery and the internal pudendal artery arise from the anterior trunk. All visceral branches are derived from the hypogastric axis.

B, type II (incidence, 20 per cent). Superior and inferior gluteal arteries arise from the posterior trunk. The internal pudendal artery and middle hemorrhoidal artery arise from the anterior trunk.

C, type III (incidence, 18 per cent). The superior gluteal artery constitutes the posterior trunk. The inferior gluteal artery and the internal pudendal artery arise independently with the anterior trunk.

D, type IV (incidence, 14 per cent). The superior gluteal artery constitutes the posterior trunk. The obturator artery, the internal pudendal artery and the inferior gluteal artery arise from the posterior aspect of a common stem which includes the anterior trunk.

E, type V (incidence, 12 per cent). The superior gluteal artery, obturator artery, inferior gluteal artery and internal pudendal artery arise from the posterior trunk.

the inner side of the bifurcation of the common iliac artery at about the level of the lumbosacral articulation. It proceeds in a downward direction on the inner border of the psoas muscle along the sacroiliac margin to the level of the sacrosciatic foramen. There the artery divides into an anterior trunk from which issue six to ten visceral branches along what may be termed the "hypogastric axis." The posterior trunk supplies the structures of the parietal pelvis and emerges from its interior into the gluteal region. The stem of the hypogastric artery is short, varies from 1 to 3 inches in length and is in inverse proportion to the length of the common iliac artery. The hypogastric artery on the right side is frequently longer than the left.

Careful surgical consideration must be given to several neighboring structures as the hypogastric arteries are prepared for ligation or occlusion by the transperitoneal approach. The posterior parietal peritoneum is opened by a T-shaped incision and peeled away from the sacropelvic wall. The terminal part of the ileum and rectum which are anterior peritoneal relations and cross over the front of the arteries

FIG. 2. Radiogram after intra-aortic injection in full-term fetus demonstrates the intact iliac arterial system. The hypogastric arteries can be identified as two vertical vessels forming an acute angle with the external iliac arteries. Note that the hypogastric arteries are wider than the external iliac arteries.

FIG. 3. Radiogram of fetus by intra-aortic injection after bilateral occlusion of the hypogastric arteries at their origin. The external iliac arteries are filled. There is marked diminution in the number of visible blood vessels in the pelvis. The hypogastric vessels are visible but have been filled through collateral channels.

are included in this displacement. The superior hemorrhoidal artery should be protected from injury as the pelvic rectum is freed along its medial border. The ureters which traverse the retroperitoneal fat in right and left oblique directions directly anterior to the arteries should be identified promptly and mobilized to their termination in the bladder especially when wide excisional surgery is intended. The

TABLE 1

LEVELS OF ORIGIN OF COMMON ILIAC ARTERY

	Shafiroff et al. (%)	Lipschutz [7] (%)	Quain [9] (%)	Dwight [10] (%)
Bifurcation of abdominal aorta:				
Opposite L_3	3	4	3	2.8
Opposite disc between L_3 and L_4	4	9	6	3.5
Opposite L_4	63	59	62	76.0
Opposite disc between L_4 and L_5	20	20	14	5.0
Opposite L_5	10	8	11	11.5
Bifurcation of hypogastric artery:				
Opposite L_5	18	14.5	..	....
Between L_5 and upper margin of sacrum	82	85.5	..	....

TABLE II
LENGTH OF COMMON ILIAC AND HYPOGASTRIC ARTERIES

Length of Common Iliac Artery		Length of Hypogastric Artery	
Author	Length (cm.)	Author	Length (cm.)
Lipschutz [7]	4 to 6 (63 %)	Lipschutz [7]	1.5 to 6.7
Henle [11]	2 to 8	Poirier [14]	2.0 to 4.0
Sappey [12]	6	Quain [9]	2.5 to 4.0
Rauber [13]	4 to 6	Shafiroff et al.	1.0 to 3.0 (21 %)
Quain [9]	2 to 5	Shafiroff et al.	3.0 to 5.0 (60 %)
Shafiroff et al.	4 to 7 (81 %)	Shafiroff et al.	5.0 to 7.0 (13 %)

iliac veins are wider and larger than the arteries and project from underneath them laterally. The obturator nerve is on the outer side of each artery embedded in fat.

The hypogastric artery and vein are enclosed in a thin but firm sheath of perivascular fascia (transversalis fascia) which can be opened by blunt dissection. This separation must be carried out with care because the thin-walled vein can be easily lacerated. The artery may be ligated in continuity or sectioned between two ligatures. Its walls should be gently but firmly approximated by a narrow umbilical tape re-enforced with one or more silk ties. Tight ligatures crush the intima and strangulate the vasa vasorum, either of which may cause delayed postoperative hemorrhage. The hypogastric arteries are ligated most effectively at their point of origin. In selected cases the anterior division of the hypogastric artery may be tied bilaterally. This should be carried out only if preoperative iliac aortograms prove the anterior division of the artery to be the sole blood supply to the pelvic viscera. Major branches distal to the site of ligation must be tied when cut in order to obviate hemorrhage from these open vessels when the collateral circulation becomes effective. The internal iliac vein need not be ligated but this is usually necessary when exenteration is performed.

The secondary blood supply to the pelvis consists of collateral pathways to the anterior and posterior trunks of the hypogastric artery and an extensive circulation across the midline. (Fig. 5.) Unilateral occlusion produces temporary circulatory disturbances with compensation obtained quickly across the midline from the opposite artery. Owen [8] describes in detail an interesting dissection of the pelvis at autopsy ten years after ligation of a single

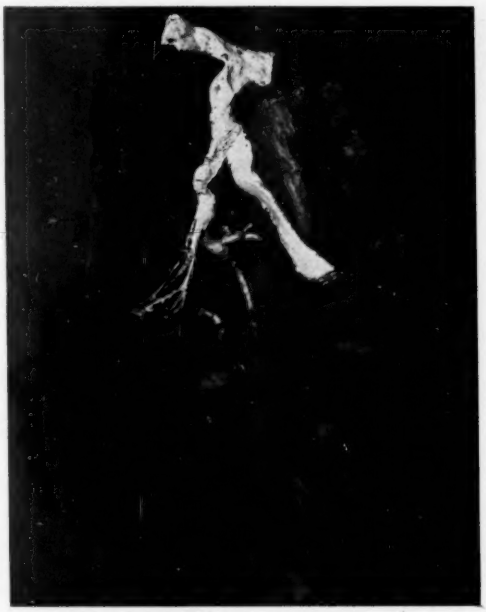

FIG. 4. Photograph of a dissected cadaver showing the pelvic basin open with the branches of the hypogastric artery *in situ*. Arteries are painted white.

hypogastric artery. Occlusion of both hypogastric arteries practically eliminates the cross circulation of blood and compensation becomes dependent on anastomotic channels from the lumbar artery, the middle sacral artery, the superior hemorrhoidal artery and branches of the external iliac artery. (Fig. 5.) The supply from these channels is at first limited and temporarily the effect is that of oligemia or ischemia. During this acute phase, the surgeon can perform radical operative procedures in the pelvis. Figure 5 shows the alternate anatomical pathways following bilateral occlusion of the hypogastric arteries.

EXPERIMENTAL LIGATION OF HYPOGASTRIC ARTERIES

The hypogastric arteries were ligated experimentally in a series of twelve dogs. (Fig. 6.) In eight animals the arteries were ligated in continuity, and in the other four the arteries were sectioned between sutures. In two animals from each of these groups, the concomitant iliac veins were also ligated. Following occlusion of the arteries a marked blanching of the pelvic viscera was noted, the blood vessels

TABLE III

VARIATIONS IN ORIGIN OF SEVERAL SURGICALLY IMPORTANT BRANCHES OF THE HYPOGASTRIC ARTERY

Artery	Major Variations* (origin from)	Minor Variations† (origin from)
Middle hemorrhoidal (present in 84% of dissections)	Internal pudental artery, inferior gluteal artery, anterior part of trunk	Obturator artery, deferential artery
Obturator	Common trunk with inferior epigastric artery, common trunk of superior and inferior gluteal arteries, internal pudendal artery	Common trunk of superior and inferior gluteal artery and internal pudendal artery
Prostatic	Anterior part of trunk, middle hemorrhoidal artery, inferior gluteal artery, inferior vesical artery	Obturator artery, umbilical artery, ischiopudendal trunk
Inferior vesical (present in 78% of dissections)	Anterior part of trunk, umbilical artery, prostatic artery, vaginal artery	Vesiculodeferential artery, internal pudendal artery
Superior gluteal	Posterior part of trunk, common trunk with inferior gluteal artery	Common trunk with inferior gluteal and obturator arteries and internal pudental artery
Inferior gluteal	Ischiopudendal trunk, anterior part of trunk, common trunk with superior gluteal artery	Common trunk with superior gluteal artery and internal pudendal artery and obturator artery
Internal pudendal	Ischiopudendal trunk, anterior part of trunk	Middle hemorrhoidal artery, uterine artery, common trunk with gluteal artery
Uterine	Anterior part of trunk, internal pudendal artery, inferior vesical artery	Obturator artery, middle hemorrhoidal artery
Vaginal (homologue of prostatic artery)	Uterine artery, anterior part of trunk, ischiopudendal trunk, inferior gluteal artery	Obturator artery, internal pudendal artery
Deferential (homologue of uterine artery)	Anterior trunk, part of internal pudendal artery, prostatic artery	Middle hemorrhoidal artery (replaced internal spermatic artery)

* Incidence greater than 10%.
† Incidence less than 10%.

became non-pulsatile and pressure fell to an average of 30 mm. Hg. Blood pressure in the external iliac artery and in the abdominal aorta increased about 20 to 40 mm. Hg above the initial values. The distal segment of the hypogastric artery and several peripheral branches were cannulated and yielded a faint trickle of blood which when collected in a beaker averaged 5 to 15 drops per minute. Three dogs were reoperated upon within forty-eight hours after the occlusion and in these the rate of flow from the distal arteries increased up to about 50 drops per minute and pulsations were absent. The remainder of the dogs were sacrificed after a period of two weeks. In these, the pelvic viscera appeared well vascularized with normal tone and pink color. Pulsations in the involved vessels were again palpable but were reduced in intensity. On cannulation of the distal segment of either hypogastric artery, blood was collected at the rate of 60 to 80 drops per minute. Angiograms were taken with 70 per cent Diodrast® injected through the abdominal aorta above the occlusion and through a site just distal to the ligation. These radiograms showed adequate

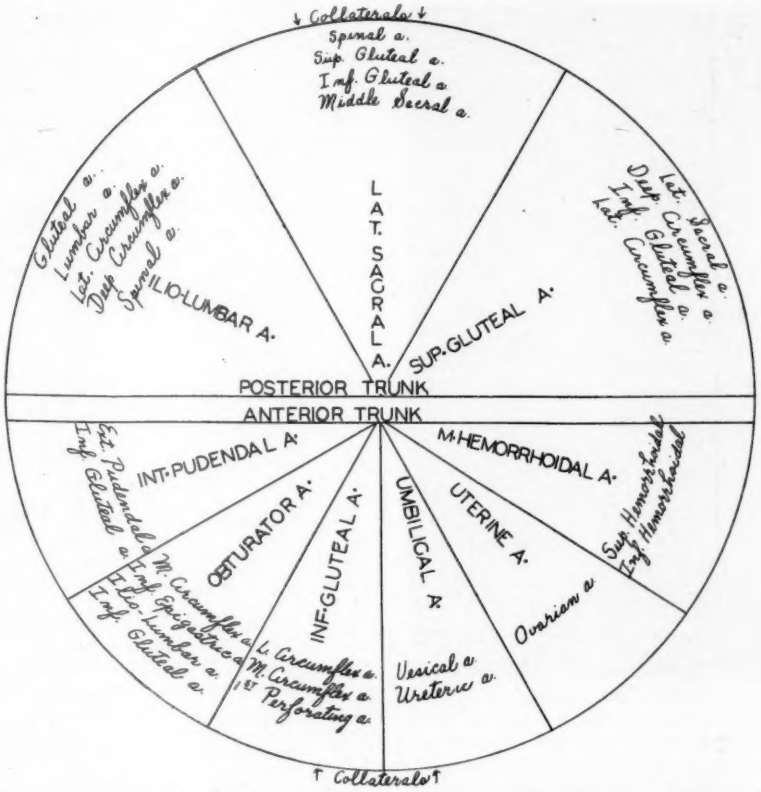

FIG. 5. Diagram of the collateral vessels to the principal branches of the hypogastric artery. Each section within the inner circle corresponds to a branch of the hypogastric artery. The outer circle contains the names of the extrailiac collateral channels to each branch. An adequate supplemental blood supply to the pelvic structures can be developed in the presence of bilateral occlusion of the hypogastric arteries.

vascularization of the pelvic organs and tissues through well formed collateral channels. The autopsies included examination of the interior of the hypogastric arteries and their branches which except for the region of occlusion, failed to show thrombi or areas of thrombosis.

CLINICAL APPLICATIONS

Bilateral ligation of the hypogastric arteries was performed in thirty-eight patients in conjunction with radical surgery for advanced carcinoma of the rectum. The inclusion of this procedure made possible the excision of pelvic viscera *in toto* or in part, the excision of segments of the levator diaphragm and the dissection *en bloc* of pelvic lymph nodes. Local necrosis in the perineum, disturbances of bladder function or impairment of the circulation in the lower extremities did not occur.

Bilateral ligation was performed successfully as an emergency operation in four patients with serious recurrent hemorrhage after total hysterectomy. In each, all other measures for control of bleeding had failed including local ligations at suspected sites of hemorrhage.

SUMMARY

1. Dissections of the iliac arterial system of cadavers were studied from the standpoint of practical application to surgery.

2. Bilateral ligation of the hypogastric arteries, was performed in twelve dogs and the physiological effects of these occlusions were noted.

FIG. 6. Radiogram of dog shows injection through the abdominal aorta immediately after operation. The collateral pathways have not yet become effective.

3. Clinical application of this procedure was made in thirty-eight operative patients with advanced carcinoma of the rectum and in four patients with postoperative hemorrhage from an undetermined source after hysterectomy.

4. Bilateral occlusion of the hypogastric arteries, temporary or permanent, offers important advantages in gynecologic and urologic surgery as well as in the general surgery of the pelvis.

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Management of Placenta in Cesarean Section

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THE once fearful death rate of patients undergoing cesarean section has grown steadily less. In 2,693 consecutive operations performed in Brooklyn during 1954, the mortality was 0.1 per cent [6]. The perinatal mortality, however, remained high, with two-thirds of the deaths associated with antepartum hemorrhage and previous cesarean section. This report is concerned principally with the relation of this area of perinatal mortality to early ligation of the umbilical cord and loss of fetal blood from the placenta. Technical details of cesarean section have been debated for generations, yet ligation of the cord has been taken for granted. The placenta itself has had considerable attention but not from the viewpoint of the infant.

Early surgeons were fearful of cutting through the placenta, believing this to be one of the greatest dangers of the operation [21]. Porro [15] incised the uterus obliquely from left to right in an effort to avoid the placenta. Kehrer [21] first to perform the low transverse incision, said that one of its advantages was that the placenta would be seldom encountered.

From the earliest times the placenta was speedily removed, until in 1803, Stein [21] brought the umbilical cord through the cervix with a small curved stick, for vaginal delivery later. In the modern era, Kerr [11] removed the placenta vaginally, except in elective section or operation performed early in labor.

It has been shown [5,6], and it is we think generally accepted, that the baby loses about 100 cc. of blood into the placenta, approximately 25 per cent of the blood volume, when the cord is clamped before pulsation ceases. Whether this is a blood loss comparable to hemorrhage, whether its return to the infant is unwise, and what its implications are in prematurity are considerations of great importance. The evidence cannot be measured until more quantitative data are available but it should be closely examined.

Suspension of the placenta still attached to the baby until pulsations have ceased or stripping of the cord are recommended by Duckman [4], Landau et al. [12], McCausland et al. [13] and others on the basis that blood is otherwise lost into the placenta. Stevenson and Erhard [18] however, believe that the baby has no immediate need of this blood and that this unduly complicates cesarean section and necessitates extra handling of the infant.

It has been established that hemoglobin levels are lower when the cord is ligated before cessation of pulsation, and iron deficiency anemia has been found in these babies months later [20]. Sidall and West [17] reported on seven babies with low hemoglobin in the first day of life; six of the cases were attributed to blood loss due to incision of the placenta. Wickster [19] has emphasized the role of post-hemorrhagic anemia and shock in neonatal death associated with antepartum hemorrhage, quoting Wiener, Macafee, and others as of the same opinion.

Neligan and Russell [14] believe that blood loss from the fetal circulation is a serious hazard of cesarean section through the lower segment for placenta previa. When the placenta was encountered they found that the operation involved a risk of damage in nearly half their patients. They quickly bring the face of the fetus into the uterine wound and clamp the cord at once before completing delivery.

Gunther [9] has shown that in vaginal delivery before ligation of the cord, although blood flow is mostly to the baby, rapid loss from baby to placenta often takes place, sometimes equalling or even exceeding the gain. Her records show that if the cord is left untied, blood vol-

* Deceased.

ume in the baby will usually increase significantly and the baby will thus be protected from dehydration during the first few days of life and from iron deficiency later.

That risk is incurred by the fetus when blood is lost from the placenta is recognized by authors of the three obstetric texts in common use. Eastman [5] sees no reason to invade the placental site when it can be avoided. Greenhill [7] promptly clamps the umbilical cord before delivery if he should incise the placenta in cesarean section for placenta previa; otherwise he lowers the baby and waits for pulsation to stop. If the greater part of the placenta is on the anterior wall of the uterus he quickly bores through it and delivers the baby by version as in the classical operation. Beck and Rosenthal [2] hold the baby below the placental level and delay ligation. In the premature infant the cord is ligated but left very long and kept sterile and warm with the placenta; its blood is subsequently injected into the umbilical vein.

COMMENTS

The immediate cause of perinatal death is all too often beyond our understanding, more difficult to determine than the cause of maternal death. When the only indication for operation is previous cesarean section, for example, it would appear that anesthesia must play an important part as a cause of apnea, yet proof is seldom possible.

In the course of pelvic delivery the placenta is often completely separated and in the birth canal drains itself of blood before delivery. When cesarean section is performed, raising the baby above the level of the abdomen, removing the placenta hastily or tying the cord promptly will deprive the infant of blood which it may need. Similarly, incision through the placenta should be avoided whenever possible. If the placenta should be encountered in the course of cesarean section through the upper or lower segment, great pains should be taken to avoid it.

Very little blood passes through the fetal lung. The fetus, often unready for birth yet summarily delivered through the abdomen, will not breathe until its blood stream is promptly rerouted. Blood must not only fill the pulmonary reservoir but must keep it full. If the first breath is deep with the strong cry of established respiration, the lungs will expand like the sudden unfolding of a crumpled paper bag [10]. Even the premature infant may cry vigorously before it is completely born. This is not always true, however. The pattern must depend to a large extent upon the maturity of the lung. In the premature infant air may not readily make its way through the bronchial tree, and many alveoli will remain non-aerated and collapsed [8]. How much blood is required to bring about ventilation is not known but it must be found in the volume available.

Within a minute or two, the foramen ovale and the ductus arteriosus cease to function [16]. Arterial blood pressure is suddenly reduced. Venous pressure remains comparatively high, distending the cord veins with blood and varying little with the cord length. The flow through these distended vessels will vary with the difference in pressure between the two ends [16]. Even a slight difference will encourage free flow. Blood may remain in the placenta or flow into the baby depending upon the time of ligation of the cord; and if the infant is held above the operative field as it so often is in cesarean section, blood flow into the placenta may be great.

The hyalin membrane syndrome which appears to be initiated with the first breath may be due to transudation resulting from increased pulmonary capillary pressure following early ligation of the cord.

SUMMARY

Miscellaneous events relating to the importance of placental blood in reduction of perinatal mortality and previous cesarean section have been presented in fairly orderly sequence. It is of course not necessary to agree with all the deductions, but it is not unreasonable to suggest that we conform more closely to the natural mechanism which appears to drain the placental compartment. As yet the worth of placental transfusion cannot be stated with certainty.

Under some circumstances blood lost from the placental circulation may result in severe fetal blood loss, even exsanguination and shock.

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Effects of Ligation of Hepatic Artery in Rabbits: Influence of Penicillin and Streptomycin

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THE dual nature of the hepatic circulation has always created interest. Liver necrosis and usually death result from ligation of the small hepatic artery, bringing relatively less blood to the liver under higher pressure; ligation of the large portal vein, supplying more blood but under lower pressure, produces relatively minor effects [5,10,12,16,22,29,31,32]. Death from hepatic necrosis and autolysis has been attributed to toxemia or infection. It has also been questioned whether arterial blood is essential for survival of the liver, or whether the liver can survive on portal blood alone if the supply of that is adequate. Tanturi, Swigart and Canepa [34] demonstrated in this laboratory that penicillin therapy enabled dogs to survive hepatic artery ligation with no significant changes in the liver, supporting the infection theory. Similar studies were carried out in dogs by Markowitz, Rappaport and Scott [24,25] and Lewis and Wangensteen [20] with comparable results. Their work stimulated interest in studying this problem in rabbits for comparative purposes.

EXPERIMENTAL STUDIES

Anatomy

The distribution of the hepatic artery and all of its branches to the five lobes of the rabbit's liver was studied by injecting a red lead suspension into an isolated segment of the aorta in seven rabbits sacrificed by bleeding under intravenous Nembutal® anesthesia. Microscopic studies in three of these rabbits revealed all hepatic arterial branches filled except the intralobular sinusoids. (Fig. 1.) The distribution of the coeliac axis closely approximates human anatomy. The diagram (Fig. 2) indicates the constant branches of the hepatic artery, as well as all variations and anomalies found. With minor exceptions, the duodenal branch of the lesser hepatic artery and the vessels to the two isolated liver lobes were the only variations in the extrahepatic arterial blood supply to the liver in the rabbit as compared to that in man. In only one rabbit was there any communication between the hepatic and the diaphragmatic or esophageal circulations.

Method of Ligation of Arterial Blood Supply to Liver

Fasting stock rabbits weighing between 5 and 10 pounds were used. Aseptic surgery was accomplished under Nembutal sedation (3/8 gr. per pound of body weight), with local 1 per cent procaine anesthesia of the anterior abdominal wall, through a midline incision from the xiphoid to the umbilicus. Cholecystectomy was performed routinely to obviate postoperative rupture of the devascularized gallbladder. All vessels to be occluded were doubly ligated and divided.

All the actual and potential sources of extrahepatic collateral arterial circulation, found to be quite constant by the anatomical studies and listed in Table 1, were carefully ligated to deprive the liver entirely of arterial blood. The methods used to accomplish this in all twenty-six rabbits in this series are diagrammed in Figure 3. Only rare variations from the normal were observed.

Injection of red lead suspension in thirteen of these twenty-six rabbits at autopsy demonstrated the success of this method. Severe necrosis obviated injection in the other rabbits.

TABLE I
POTENTIAL SOURCES OF EXTRAHEPATIC COLLATERAL ARTERIAL CIRCULATION TO THE LIVER OF THE RABBIT

Common hepatic artery:
Right gastric artery
Gastroduodenal artery
Retroduodenal branches (small)
Proper hepatic artery:
Portal vein branches (minute)
Common bile duct branches (minute)
Direct communication with gastroduodenal artery (isolated case)
Lesser hepatic artery:
Duodenal branch (present in 91 per cent of cases)
Left hepatic artery:
Communication with left inferior phrenic artery through esophageal plexus (isolated case)

Only four rabbits had some persistent arterial blood supply to the liver, as depicted in Figure 4. Minute arterial branches, which were not ligated, dilated to provide collateral circulation in three rabbits. New, tortuous vessels formed from the still ligated and divided stumps of arteries in two rabbits. There were no collaterals from diaphragmatic vessels. Dense, vascular adhesions involved partially autolyzed livers in rabbits with prolonged survival times, but no vessels from these adhesions could be demonstrated actually entering the liver.

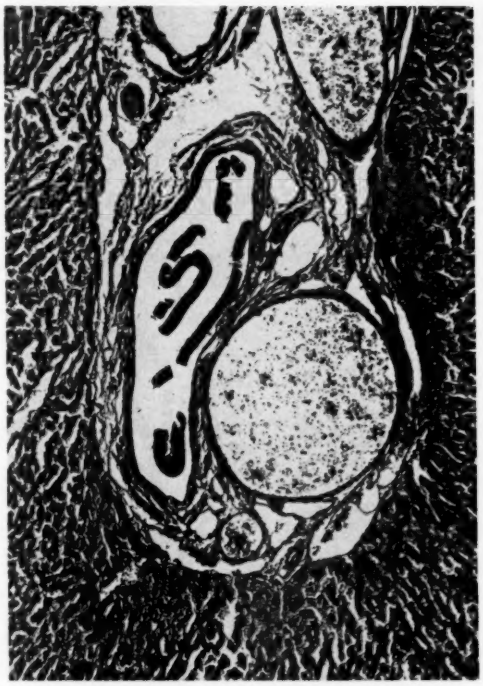


FIG. 1. Photomicrograph of liver of rabbit following injection of hepatic artery with red lead suspension injection mass for anatomical study. The granules of the injection mass may be seen with ease in the larger and smaller arterial branches in this portal canal. Hematoxylin and eosin stain.

RESULTS

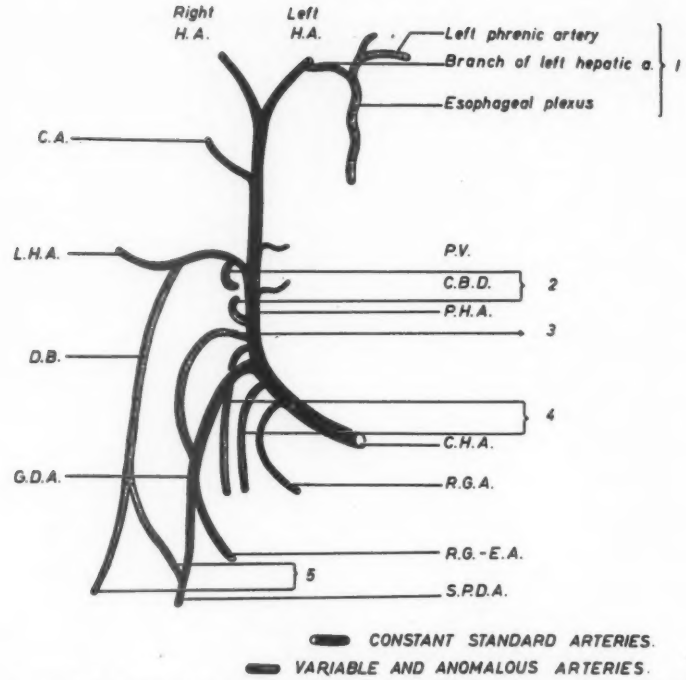
Eighteen of these twenty-six rabbits survived the surgery uneventfully. Six rabbits in group I received no special treatment postoperatively. In group II there were five rabbits; each received 300,000 units of aqueous procaine penicillin intramuscularly twice daily for about ten days. Group III, comprised of the remaining seven rabbits, received penicillin in this manner plus intramuscular dihydrostreptomycin sulfate, 0.25 gm. twice daily for ten days. The mortality statistics of the twelve rabbits which subsequently died are tabulated in Table II.

Group I. The results obtained in this group, which received no antibiotics, are summarized in Table III. Five of the six rabbits died in an average of 5.8 days.

The three which died earliest lived an average of 4.3 days, with evidence of definite gas bacillus infection at autopsy: crepitant liver, free gas and hemorrhagic fluid in the peritoneal cavity. Grossly, necrosis and large anemic infarcts involved the liver, with generalized degeneration, edema, congestion and increased friability. Microscopic study revealed the bloodless areas of necrosis with marked parenchymal degeneration. The sinusoids and portal vein tributaries and, to a lesser extent, the central veins were dilated. Large numbers of bacilli (Fig. 5) were present in all three of these livers but in no others of the entire study.

The other two rabbits which died in group I lived an average of eight days, with no evidence of gas infection. Marked hepatic degeneration was present, with softening, congestion, adhesions, anemic infarcts and abscess formation. Similar but less marked microscopic changes were seen.

Rabbit 17 survived with no antibiotics until it was sacrificed on the fifty-sixth postoperative day in good condition. Significant arterial circulation to the liver was not present, and there was massive autolysis of the entire main cephalad liver mass. Rounded edges indicated hy-



KEY: C.A., cystic artery. C.B.D., branch to common bile duct. C.H.A., common hepatic artery. D.B., duodenal branch of lesser hepatic artery. G.D.A., gastroduodenal artery. L.H.A., lesser hepatic artery. Left H.A., left hepatic artery. P.V., branch to portal vein. R.A., retroduodenal artery. R.G.A., right gastric artery. R.G.-E.A., right gastroepiploic artery. Right H.A., right hepatic artery. S.P.D.A., superior pancreaticoduodenal artery.

FIG. 2. Anatomical distribution of hepatic artery, including standard branches constant in all rabbits and all variable and anomalous vessels demonstrated. (1) Indirect connection between left inferior phrenic and left hepatic arteries through esophageal plexus. Isolated case, only anastomosis between hepatic and diaphragmatic circulations demonstrated in thirty-three rabbits. (2) Branch to caudate lobe, present in all rabbits, arising from proper hepatic or lesser hepatic artery. (3) Direct connection between proper hepatic and gastroduodenal arteries. Isolated case. (4) Retroduodenal artery, present in three rabbits, arising from common hepatic or proper hepatic artery. (5) Duodenal branch of lesser hepatic artery, present in all but three of thirty-three rabbits, anastomosing directly or through capillary connections with superior pancreaticoduodenal artery.

pertrophy of the right posterior and caudate lobes. Areas of complete necrosis with leukocytic infiltration, and marked bile duct proliferation and fibrosis with dilated, engorged blood vessels in the areas of regeneration were seen microscopically.

Group II. The results obtained with five rabbits given penicillin postoperatively are summarized in Table IV. Four died an average of 15.3 days after surgery. The mortality rate of group II approximated that of group I, but the survival times of the former were significantly greater.

The postoperative courses of rabbits 4 and 15 were similar to those of medium survival in group I, with comparable survival times and gross and microscopic appearances. There was no evidence of gas infection.

Rabbits 5 and 6 survived an average of 21.5 days, with lethargy, weakness and weight loss terminally. Large areas of necrosis and autolysis involved the livers, but there were more adhesions about the livers and more evidence of regeneration. The microscopic picture revealed congestion and dilatation of portal vessels, with the bloodless necrotic areas walled off by leukocytic infiltration and fibrous tissue.

In rabbit 15 lethargy and weight loss developed just prior to sacrifice on the fifty-eighth day after surgery. Only a minute amount of arterial blood was reaching the liver and much liver autolysis was present, but there

was a considerable degree of compensatory regeneration.

Group III. Table v summarizes the results with the seven rabbits which received both penicillin and streptomycin postoperatively.

Three survived only an average of 4.7 days, although there was no evidence of gas bacillus infection. All three had gastric dilatation with thinning of the fundus, which perforated in two, as was also noted in some rabbits with the shortest survival times in groups I and II. The courses and findings in these group III rabbits approximated those in group I and II rabbits which died in about ten days of aseptic autolysis and hepatic insufficiency, with some infection possibly present. Figure 6 shows the typical microscopic appearance.

Four rabbits survived indefinitely until sacrificed between six and sixteen weeks after surgery. All went through a period of weakness, lethargy and weight loss, but recovered well. There was a high degree of infarction and necrosis undergoing autolysis and calcification. Remarkable compensatory hypertrophy restored almost the normal amount of liver, in spite of the essentially complete lack of arterial blood. Figure 7 reveals the marked bile duct proliferation, fibrosis and leukocytic infiltration in the portal canals seen in these livers. The large areas of necrosis and autolysis had lost almost all semblance of normal hepatic architecture, but the regenerated areas in the rabbits that lived the longest approached normal liver structure except for some centrilobular vacuolation, cloudy swelling and sinusoidal congestion.

Liver Function Studies

Icterus indices performed on a Coleman universal spectrophotometer on five control animals indicated that 5 was the upper limit of normal in the rabbit. Of the four rabbits that failed to survive hepatic artery ligation on whom determinations were done, the icterus index was elevated in all cases. Multiple determinations on six rabbits which survived until sacrificed were all normal with one exception, done immediately after a period of weakness and lethargy interpreted as liver insufficiency. Hepatic insufficiency is thus further suggested as the cause of the spontaneous deaths.

COMMENTS

A technic of hepatic artery ligation, to include all potential sources of collateral arterial circulation, was successful in depriving the rabbit's liver of all arterial blood in most instances. Only minimal collateral circulation developed. In prolonged experiments, new vessels can form from the ligated stumps of divided arteries to supply the liver anew with arterial blood. Diaphragmatic vessels are not an important source of collateral arterial circulation to the liver in the rabbit, and even dense adhesions failed to supply the liver with significant amounts of blood, although these were impor-

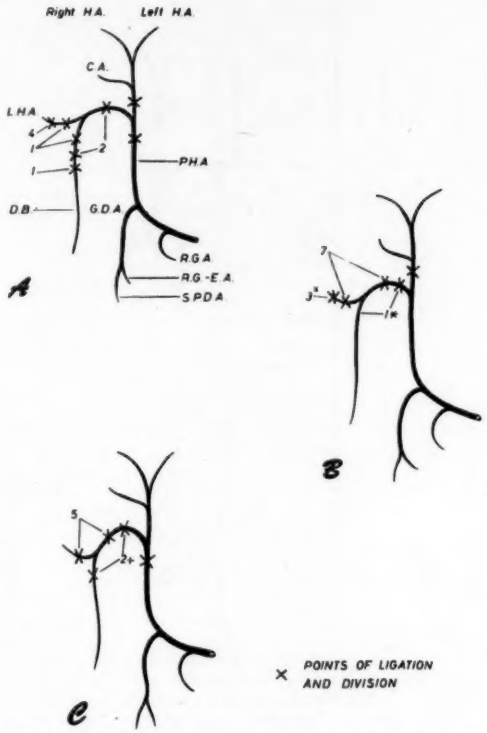


FIG. 3. Methods of ligation, and division or excision of the hepatic artery used to deprive the liver of arterial blood completely. (Lesser hepatic artery and its duodenal branch controlled, as diagrammed, by one or two points of ligation in each rabbit.) Labels of vessels as in Figure 2. A, proper hepatic artery ligated both proximal and distal to lesser hepatic artery (eight rabbits). B, proper hepatic artery ligated only distal to lesser hepatic artery (eleven rabbits). C, proper hepatic artery ligated only proximal to lesser hepatic artery (seven rabbits). * Two duodenal branches present in this rabbit; both ligated. × One of these rabbits had no duodenal branch. + One of these had two lesser hepatic arteries, each with a duodenal branch; all four vessels ligated. The other had multiple duodenal branches of the lesser hepatic; all were ligated.

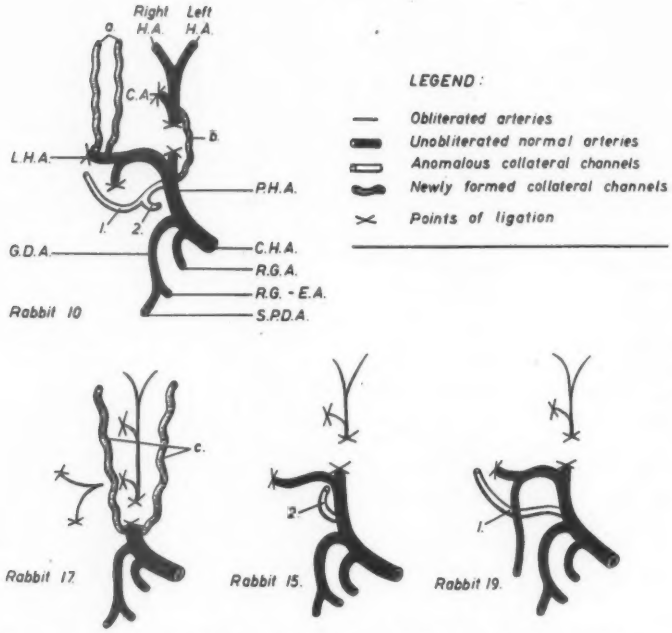


FIG. 4. Sources of arterial blood to the livers of the four rabbits in which persistent hepatic arterial blood supply was demonstrated after ligation. (Vessels labelled as in Figure 2.)

tant sources of collateral arterial blood in the dog [*19,21,30,38*].

Eighteen rabbits which survived the surgery were studied. Three of the six rabbits which received no chemotherapy died early with overwhelming anaerobic gas bacillus infection, such as that previously observed by so many [*14,15, 18,37*]. The administration of penicillin, especially when combined with streptomycin, consistently prolonged life and sometimes permitted indefinite survival following hepatic artery ligation; in none of these animals did

TABLE II

MORTALITY RATES OF RABBITS FOLLOWING HEPATIC ARTERY LIGATION, ACCORDING TO CAUSES OF DEATH AND POSTOPERATIVE TREATMENT

	Death Due to Gas Bacillus Infection		Death Due to Aseptic Autolysis and Hepatic Insufficiency				Total	
			Early with Probable Low Grade Infection		Late with No Evidence of Infection			
Group I, 6 rabbits								
No treatment postoperatively	3	50%	2	33%	0	....	5	83%
Group II, 5 rabbits								
Penicillin postoperatively	0	....	2	40%	2	40%	4	80%
Group III, 7 rabbits								
Penicillin and streptomycin postoperatively	0	....	3	43%	0	....	3	43%
Total, 18 rabbits	3	17%	7	39%	2	11%	12	67%

TABLE III
SUMMARY OF RESULTS IN GROUP I, WITH NO ANTIBIOTICS

Rabbit No.	Sex, Weight (lb.)	Survival (days)	Type of Ligation (Fig. 3)	Course, Cause of Death and Remarks
1	M, 7	6	A	Uneventful; condition good 24 hr. before death; aseptic autolysis and hepatic insufficiency with probable low grade infection; no collateral circulation observed, not injected; liver soft, congested, no infarcts; hemorrhagic pleural and peritoneal fluid; lungs wet; gastric fundus perforated
2	F, 9	10	C	Condition good 24 hr. before death; aseptic autolysis and hepatic insufficiency with probable low grade infection; no collateral observed; large hepatic infarcts and abscesses; lungs hemorrhagic
3	F, 8	5	A	Uneventful; condition good 2 hr. before death; gas bacillus infection; no collateral observed; liver necrotic, crepitant; peritoneal gas; hemorrhagic peritoneal and pleural fluid; lungs hemorrhagic; kidneys crepitant; bacilli in liver (Fig. 5)
7	F, 8	4	A	Condition good 24 hr. before death, except for purulent nasal discharge; gas bacillus infection; no collateral observed; liver soft, edematous, congested, large anemic infarcts with surrounding gas; peritoneal gas and fluid; lungs hemorrhagic; gastric fundus perforated; bacilli
16	M, 8½	4	A	Uneventful; condition good 48 hr. before death; gas bacillus infection; no collateral observed; liver necrotic, crepitant, infarcted; portal vein dilated; bloody bile in bile ducts; peritoneal gas and fluid; lungs and pleura hemorrhagic; kidneys and spleen crepitant; gastric fundus thin but intact; bacilli in liver
17	M, 8½	56 (sacrificed)	A	Uneventful; condition good throughout; maintained initial weight of 8½ lb. at death; sacrificed while in good condition; injection demonstrated newly formed collateral channels (Fig. 4); aseptic autolysis of entire main liver mass, with thick capsule; other liver lobes showed marked hypertrophy, congestion, with anemic infarcts

frank gas infection develop in spite of extensive liver necrosis. Deaths in these rabbits could be attributed to liver insufficiency from deficient circulation *per se*, toxemia from the necrotic liver, or a less virulent bacterial infection which increased oxygen demands and produced a relative oxygen deficiency with resulting liver failure. Antibiotics permit survival by controlling infection, allowing time to establish compensatory circulation.

Even in the absence of gas infection, true aseptic autolysis of the liver occurs as a result of ischemia and anoxia, but aseptic autolysis itself does not cause death. For survival, sufficient circulation must be retained to maintain liver function at a level compatible with life, either through collateral arterial circulation or through the portal vein. Arterial blood is not essential for preservation of the rabbit's liver, but a sufficient oxygen supply is. If bacterial infection were the cause of the massive necrosis and autolysis seen in the animals that survived, death would have been almost inevitable. The indefinite survival of six rabbits with massive liver necrosis argues against toxemia from aseptic autolysis of the liver being a major factor in the death of such animals, in spite of the conclusions of many previous workers [*1,4,27,35*].

Liver insufficiency is believed to have played a primary role in the death of those rabbits with much liver degeneration and no evidence

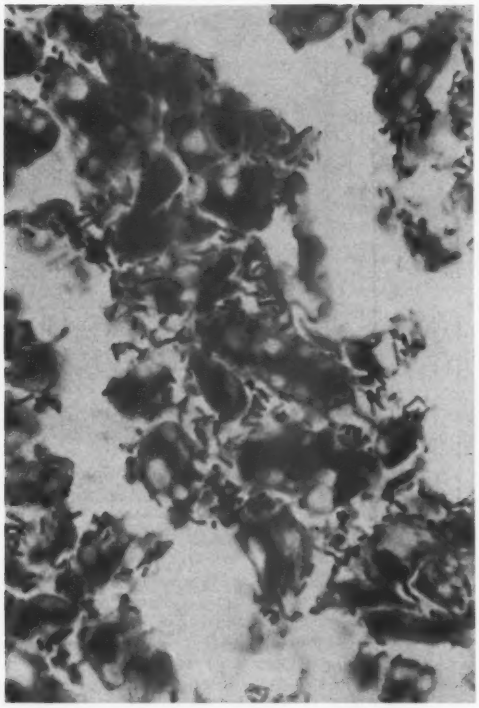


FIG. 5. Photomicrograph of liver of rabbit 3, group I, which died of gas infection in five days. Enlarged to show the overwhelming numbers of bacilli in the liver. Hematoxylin and eosin stain.

FIG. 6. Photomicrograph of liver of rabbit 11, group III, which died spontaneously in three days, quite typical of early death without gas infection. To the right is seen the edge of a necrotic infarct, with marked cloudy swelling, cellular degeneration and loss of normal hepatic architecture. On the left is noted marked sinusoidal and some portal vein dilatation, but degeneration of the walls of the portal vein branches with thrombosis has occurred. Hematoxylin and eosin stain.

of infection, in spite of the high functional reserve of the liver. Almost all the rabbits which died spontaneously, except those with obvious gas infection, had anorexia, weight loss, weakness, lethargy and mysterious, surprisingly sudden death. These symptoms were characteristic of liver insufficiency, as noted in careful previous studies [*3,13,23*]. The rabbits of group III which survived passed through a brief period of similar symptoms, hepatic hypertrophy perhaps overcoming the liver insufficiency which caused them. The microscopic findings of hepatic degeneration correlated well with the degree of liver insufficiency suspected on this basis. Slight increases in the icterus index coincided with the periods when functional insufficiency was thought present.

Liver necrosis and death following hepatic artery ligation could be influenced by other factors serving to decrease liver circulation below the critical level. Thrombosis of inrtahepatic portal vein branches was observed, presumably due to arterial ischemia of the vein walls. Hypotension during and after surgery would decrease blood flow with resulting anoxia [*28,29*]. Shock resulting from intraperitoneal fluid loss in liver autolysis was considered a contributing factor by Mason and Lemon [*26*], but in this study such fluid loss was significant only in the three rabbits with gas bacillus peritonitis.

More detailed bacteriological studies, more thorough evaluation of the hepatic circulation and of oxygen utilization, and more complete liver function studies are required before more definite conclusions can be drawn regarding the relative importance of bacterial infection, oxygen deficiency and liver insufficiency in the results of these experiments.

Hepatic arterial and portal venous blood mix freely in the intrahepatic sinusoids, which

TABLE IV

SUMMARY OF RESULTS IN GROUP II, WITH PENICILLIN POSTOPERATIVELY

Rabbit No.	Sex, Weight (lb.)	Survival (days)	Type of Ligation (Fig. 3)	Course, Cause of Death and Remarks
4	F, 9	10	B	Uneventful; excellent condition until just before death; aseptic autolysis and hepatic insufficiency with probable low grade infection; no collateral circulation demonstrated on injection; massive hepatic infarct; rest of liver soft; lungs and pleura hemorrhagic
5	F, 8	20	A	Uneventful for 1 wk., then lethargy, weakness, weight loss; aseptic autolysis and hepatic insufficiency with no evidence of infection; no collateral demonstrated; large areas of hepatic necrosis and autolysis; hypertrophy of remainder of liver; lungs hemorrhagic; gastric fundus perforated
6	F, 8	23	B	Uneventful; in good condition 5 days before death, then weakness and weight loss; aseptic autolysis and hepatic insufficiency with no evidence of infection; no collateral observed, not injected; complete necrosis and partial autolysis of entire main liver mass; hypertrophy of right posterior lobe; portal vein branches dilated
14	F, 8	8	B	Uneventful; in excellent condition 48 hr. before death; aseptic autolysis and hepatic insufficiency with probable low grade infection; no collateral demonstrated; hepatic softening with anemic infarcts; hemorrhagic peritoneal fluid; lungs wet; gastric fundus thin but intact
15	F, 8	58 (sacrificed)	B	Uneventful; in good condition until 1 wk. before sacrifice, then lethargy and weight loss; weight 5½ lb. at death; sacrificed in fair condition; injection demonstrated minute anomalous artery to caudate lobe not ligated (Fig. 4); encapsulated autolyzing anemic hepatic infarcts; regeneration in rest of liver, with rounded edges

should permit maintenance of hepatic circulation following hepatic artery ligation. These two circulations have a mutual direct influence on each other at their point of mixing and by lateral pressure [6,17,33]. The volume flow of one is influenced by the pressure of the other, total hepatic blood flow being kept constant by reciprocal compensatory changes, as demonstrated by Burton-Opitz [6]. Arterial volume flow has more influence on portal pressure in cirrhosis than in the normal liver [7,11,12,17], which led Herrick [17] and Dock [11] to postulate that decreasing the increased hepatic arterial flow in cirrhosis should permit increased portal flow with less pressure.

The present studies suggest that increased portal vein flow is relatively more important than the sparse collateral circulation in compensating for hepatic artery ligation in the rabbit, even as Loeffler [21] concluded. Dilatation of the portal vein and its intrahepatic branches was obvious in all rabbits which died in less than a month. Although some arterial blood supply was demonstrated in three of the six rabbits which survived indefinitely, this was relatively minute and/or occurred late due to angiogenesis after survival was already assured; no arterial flow could be found in the other three. The potential collateral arterial circulation to the liver was also shown to be less in rabbits than in dogs by Cameron and Mayes [8] and McMichael [29]. Rabbits must depend on the physiological increase in portal vein flow [6], and higher efficiency in utilization of portal vein oxygen by the liver [2,18,29], to compensate for decreased hepatic artery flow.

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TABLE V

SUMMARY OF RESULTS IN GROUP III, WITH PENICILLIN AND STREPTOMYCIN POSTOPERATIVELY

Rabbit No.	Sex, Weight (lb.)	Survival (days)	Type of Ligation (Fig. 3)	Course, Cause of Death and Remarks
8	F, 7	2	C	Lethargic; aseptic autolysis and hepatic insufficiency with probable low grade infection; gastric dilatation; no collateral circulation observed, not injected; liver soft and congested with anemic infarction; lungs hemorrhagic; stomach dilated but intact
9	F, 9½	110 (sacrificed)	C	Uneventful; in good condition for 14 days, then lethargy, weakness, weight loss for 2 days; recovered good condition, gained weight till sacrificed; sacrificed in good condition; no collateral demonstrated on injection; liver small, with firm infarcts and rounded edges indicating regeneration
10	M, 8	68 (sacrificed)	B	Uneventful; in good condition for 9 days, then 3 day period of weight loss and weakness; recovered excellent condition, weight 10 lb. at death; sacrificed in good condition; injection demonstrated unligated anomalous channels and newly formed vessels (Fig. 4); large, encapsulated, necrotic, autolyzing, semiliquefied mass of liver; regeneration in rest of liver, with rounded edges
11	F, 8	3	B	Uneventful; in good condition 24 hr. before death; aseptic autolysis and hepatic insufficiency with probable low grade infection; ? gastric perforation; no collateral demonstrated; anemic infarcts of all lobes; liver soft and congested; lungs hemorrhagic; gastric fundus perforated
12	F, 7	42 (sacrificed)	B	Lethargic and weak for 6 days after surgery; then condition good until sacrificed; sacrificed in good condition; no collateral demonstrated; atrophy and firm infarcts of main liver mass; infarcts and marked hypertrophy of rest of liver
13	F, 7	49 (sacrificed)	A	Good immediate recovery from surgery, then weak, refused food from 2nd to 7th postoperative days; recovered good condition, weight 7 lb. when sacrificed; sacrificed in good condition; no collateral demonstrated; atrophy of main liver mass, with many old calcified infarcts; large encapsulated cystic mass of necrotic autolyzing infarct in main liver mass; marked hypertrophy of rest of liver; gastric dilatation
18	F, 8½	8	B	Uneventful, in good condition for 1 wk.; became lethargic and died next day; aseptic autolysis and hepatic insufficiency with probable low grade infection; ? gastric perforation; no collateral demonstrated; liver congested, anemic infarcts at edges of all lobes; portal vein branches dilated; gastric fundus perforated, ruptured through diaphragm

Higher survival rates and less liver necrosis can be expected in dogs compared to rabbits after hepatic artery ligation [*9,24,25*].

The remarkable compensatory powers of the portal vein of the rabbit in the absence of arterial flow were demonstrated. Not only was liver function maintained but also marked hypertrophy of the surviving portions of the liver was permitted to compensate for those portions that had undergone necrosis and autolysis. Such regeneration through an intact portal circulation in the absence of arterial blood has been previously demonstrated by Whipple and Sperry [*36*].

If such liver regeneration, with improved hepatic function, occurred in man through im-

proved efficiency of the portal circulation following hepatic artery ligation in cirrhosis, this procedure in the treatment of portal hypertension would be looked upon with more favor. However, fatal hepatic insufficiency may result from inadequate collateral circulation, or portal hypertension may rapidly recur due to restoration of hepatic arterial flow through angiogenesis or excessive collateral arterial blood supply.

SUMMARY AND CONCLUSIONS

1. Anatomical studies of rabbits provided a method of hepatic artery ligation which was successful in depriving the liver of all arterial blood in most cases.

2. Hepatic artery ligation was successfully accomplished in eighteen rabbits, studied in three groups: group I received no antibiotics postoperatively, with a mortality rate of 83 per cent (50 per cent due to obvious gas bacillus infection); penicillin was administered to group II, with 80 per cent mortality; group III received both penicillin and streptomycin postoperatively, with a mortality rate of 43 per cent.

3. The liver deprived of arterial blood is susceptible to fatal gas bacillus infection with massive liver necrosis. Antibiotics can control this infection and prolong life, often permitting indefinite survival by allowing time to establish compensatory circulation. Penicillin and streptomycin together are more effective than penicillin alone.

4. Ischemia and anoxia cause massive necrosis and true aseptic autolysis even in the absence of gas infection. Aseptic autolysis *per se* does not cause death. Survival depends upon sufficient circulation to maintain liver function at a level compatible with life. There was some evidence that functional insufficiency of the liver, rather than bacterial infection or toxemia, was the primary cause of death in those rabbits which died with no evidence of gas infection.

5. There is minimal collateral arterial circulation to the rabbit's liver following hepatic artery ligation. Phrenic vessels are not a significant source of collateral blood supply in the rabbit. Angiogenesis can in time provide the liver with some arterial blood. Increased portal vein flow is more important in maintaining adequate liver function and sustaining life in the rabbit. Portal circulation was sufficient to permit compensatory hypertrophy of the rabbit's liver in the absence of arterial blood.

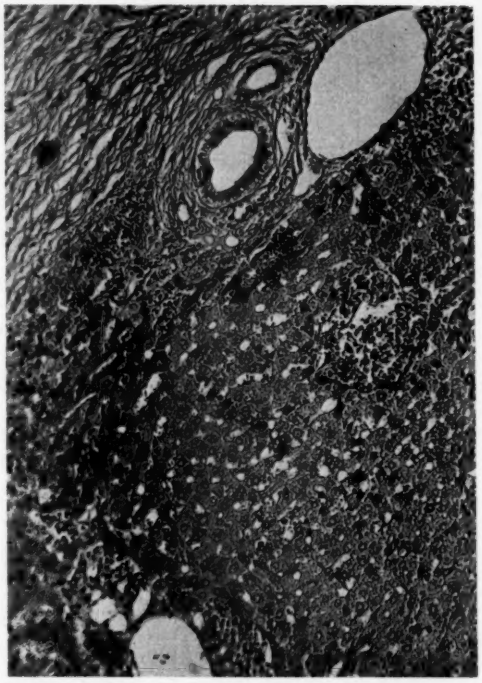

FIG. 7. Photomicrograph of liver of rabbit 12, group III, which was sacrificed after surviving forty-two days, representative of prolonged survival. Above on the left is the thick fibrous capsule of an infarct. Cellular degeneration, vacuolation and cloudy swelling are present but considerable proliferation of bile ducts is observed with sinusoidal and portal vein dilatation. Hematoxylin and eosin stain.

Arterial blood is not essential for preservation of the rabbit's liver.

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SURGICAL REVIEW

Transplantation of Tissues

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"By medicine life may be prolonged, yet death will seize the doctor, too."
William Shakespeare, "Cymbeline."

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TRANSPLANTATION of tissues is not a new field [1]. The Egyptians as far back as 3500 B.C. were concerned with the correction of noses laid waste by syphilis and the Sacred Vedas mention grafting operations among the Hindus at approximately the same time. The art spread from Egypt and India to the southern parts of Asia, to Persia and Arabia, and then to Greece, diffusing into Italy as an aftermath of the Roman Wars.

Celsus and Galen [1] were the transplantation scholars of the period between 53 B.C. and 210 A.D. The former wrote in "De Medicina" that tissues could be transplanted from one part of the body to another and flourish in their new location. Galen gave instructions for the repair of facial defects. From his death to the fifteenth century no contributions were made in the field of tissue transplantation.

Rosano [1], Bishop of Lucera, recorded in his "Annals of the World" that a doctor named Branca in 1442 reintroduced the Indian flap method for repairing facial defects using skin from the cheek and forehead.

The use of skin flaps from the arm is widely credited to Tagliacozzi [1], Professor of Anatomy at Bologna, who described the technique in 1597. Pressure from theologians at that time who censured him for "interfering with the handiwork of God" brought about the death of the operation with the author. When the British East India Company penetrated India, information on the Indian forehead flap was brought back to England. This was followed by a rash of reports in British, French and German literature in the nineteenth century.

The art of transplantation of free tissue flourished in the period between 1850 and 1900 [1]. Sancassaire narrates the tale of a street vendor who applied an unusual gimmick to her trade. She would cut a piece of skin from her leg, pass it around the audience on a plate, replace it, and cover it with her magic salve. It was said that the operative area was barely discernible. In 1869 Reverdin [1], a Swiss surgeon, successfully transplanted living pieces of epidermis to a granulating area, and Ollier in 1872 [1] suggested the use of sheets of skin including not only the epidermis but parts of the dermis. It was Thiersch in 1874 [1] who removed the granulation tissue and covered the entire wound with strips of epidermis. Wolfe in 1875 [1] and Krause in 1893 [1] described methods for free full-thickness grafts.

At the turn of the nineteenth century techniques for transplantation of vessels and organs were developed by Carrel [2] and in 1906 Zirm [3] successfully homografted a cornea.

The results obtained by Carrel and Lindbergh [4] in 1938 on maintaining the viability of

human organs *in vitro* opened up an important possibility which has not been adequately pursued. Carrel's dream was to remove diseased organs, treat them energetically in the Lindbergh pump, and reimplant them.

A theory to explain the mechanisms involved when homografts are rejected was proposed by Loeb in 1944 [5]. Writing on the biological basis of individuality, he stated his concept that a local cellular reaction accounted for the failure. Loeb's idea was that "genetic factors lead to the production of substances which when introduced into organisms possessing different organismal differentials cause incompatibilities between host and transplant." Loeb believed that the organismal differentials were direct cytotoxins which brought about a "round cell infiltration around the homotransplant." We agree with Dempster's [6] appraisal that "Loeb's writing and theory are difficult to understand and follow." Additionally, other work seriously questions the validity of the local cellular reaction theory. In 1943 Harris [7] showed that rat and mouse cells were apparently physiologically compatible *in vitro*. Toxic phenomena were completely absent in mixed culture. These experiments demonstrated complete neutrality between rat and mouse cells maintained in close culture association. If, indeed, "organismal differentials" were present, they were at least elusive in Harris's laboratory. Medawar's work, which forms the basis of the currently accepted theory of the rejection of homotransplants will be reviewed in the section on the theory of actively acquired immunity.

Definitions. Before launching into a general discussion of the transplantation of tissues it is essential to define several terms appearing frequently in the literature on transplantation:

Autotransplant: A transplant to the same individual from whom the tissue was removed.

Isotransplant: A transplant between individuals of the same (identical twins) or nearly the same genetic background (inbred strains).

Homotransplant: A transplant between individuals of the same species but a different genetic background, as from one patient to another not his identical twin.

Heterotransplant: A transplant between members of two different species as from a rat to a dog.

"*Homostatic*" *transplant* [8]: A transplant which functions as a framework to be ultimately replaced by host tissues. It is not dependent on cell viability. Freeze-dried artery is an example.

"*Homovital*" *transplant* [8]: A transplant depending on the maintenance of cellular viability for its success. Kidney is such a tissue.

Acquired tolerance [9]: A state of reduced or absent reactivity to antigenic substances produced in a host by previous exposure of the organism in the embryonic or neonatal state to the same or closely related antigen.

"*Second set phenomenon* [10]: The occurrence of an accelerated homograft rejection reaction in an animal when a second graft is applied from the same donor.

"*Brephoplastic*" *transplant* [11]: A transplant of embryonic, fetal or newborn tissue which functions or survives in young or adult animals. (From the Greek words "brephos"—newborn, and "plassein"—to model.)

"*Adoptive*" *immunity* [12]: A resistance to transplantation which results from transfer of immunologically active lymph node cells. The term adoptive is appropriate because the transferred lymphoid cells continue for a time to function in or are adopted by the new host. (Differs from passive immunization in that an adoptively immunized animal is capable of a secondary response, and from active immunization in that the animal in question has not given a primary response [13].)

Enhancement [14]: Phenomenon of progressive tumor growth in a normally resistant animal caused by the prior injection of nonliving donor tissue.

Chimerism: Coexistence in the same animal of genetically different tissues. This state exists after radiated mice have accepted rat bone marrow.

The purpose of this review is not only to acquaint the physician with the strides that have been made in the field of transplantation of tissue but to point up the large gaps still remaining in our knowledge. It has been divided into three sections. The first deals with general problems of transplantation; the second with a more detailed approach to specific types of grafts; and the third with preservation of tissues.

At the beginning we desire to state that this is not a complete summary of the world's literature on transplantation which includes over 10,000 papers. For other reviews of the general subject the reader is referred to articles by Brown [15], Medawar [16–18], Cannon et al.

[19], Longmire [20], Longmire and Smith [21], Dempster [6], Egdahl [22,23], Cannon and Murray [24,25], Conway and Stark [26], Ferrebee and Merrill [27], Peer [28], Snell [29], and Brent [30].

To assist in this undertaking letters were written to many of the best known workers in the field of transplantation. From time to time personal communications from them will be quoted.

Theory of Actively Acquired Immunity. During the Second World War, when the demand for replacement of skin reached a peak, Medawar set out to shed light on the nature of the rejection of skin homografts and postulated his theory of "actively acquired immunity." He laid a sound experimental approach to this subject on the basis of skin homografts transplanted orthotopically (positions formerly occupied by skin). Except for the homologous transplantation of tumors, cartilage and cornea, it seems fair to state that the general problems involved in the rejection of skin probably apply to most other tissues.

In 1944 Medawar [31] demonstrated that the second set of homografts from the same donor to the same recipient disintegrated at a faster rate than the first set. He emphasized that the larger the amount of skin grafted the faster the disintegration. This dosage effect comes into play when two grafts are transplanted into an area drained by a single set of lymph nodes. The fact that the survival time of a homograft varies inversely with the quantity of tissue grafted is taken as strong evidence that intolerance to homotransplantation is acquired and not natural.

Prior to the rejection of the first set of homologously transplanted skin, a latent period exists during which homografts resemble autogenous skin grafts [10]. This latent period is said to negate the theory of natural immunity to skin grafts which would occur in incompatibility of blood transfusions when a recipient of one blood group receives a transfusion of red cells from a donor of another group.

Exposure to homologous skin leaves the recipient in a state of intolerance so that a second set of skin homografts from the same donor produces an accelerated reaction with a curtailment of survival time. This acquired immunity is noted only when skin is grafted from the same donor responsible for the immunization. It is on the basis of the aforementioned considerations that Medawar postulated that intolerance to homografts belongs in the general category of actively acquired immunity.

As to the effectiveness of different routes of immunization, Medawar [32] found that heightened resistance against homografts of skin brought about by preliminary grafting of the recipient with donor leukocytes was eighteen times more effective on a dosage basis when the leukocytes were injected intradermally than when they were given intravenously. This great disparity between the effectiveness of intradermal and intravenous routes of immunization has been cited by many workers as evidence for the similarity of transplantation immunity and delayed type sensitization reactions.

Billingham, Brent and Mitchison [33] recently compared different routes for the administration of suspensions of homologous cells in the three most common laboratory animals. In the mouse, in which suspensions of splenic cells or thymocytes were used as the antigen, all five routes tested were equally effective over a wide range. With the rabbit, however, splenic cells injected intradermally elicited a more powerful immune response than when injected intravenously, and intraperitoneal injections gave irregular results. The finding that homologous splenic cells will immunize rabbits at all when administered intravenously is of interest since both leukocytes and epidermal cells are known to be ineffective when administered by this route.

Although there is a great deal of evidence that the mechanism of homograft rejection and the delayed type sensitivity reaction are similar, particularly the fact that transplantation immunity is transferable by cells and not by immune serum [34], the Billingham report on the effectiveness of intravenous immunization weakens one of the pillars of the argument. For a review of the similarities between the rejection of homografts and tuberculin-type allergy, the reader is referred to an article by Lawrence [35].

The Medawar theory is accepted by most workers in the transplantation field. However, Dr. W. J. Dempster of the Post Graduate Medical School, London, cautions against its complete acceptance. In a personal communication to us he wrote: "For some time now I have been preaching against the actively acquired immunity theory which appears to be accepted so uncritically everywhere. There is no evidence

of an antigen-antibody reaction when a first homologous kidney transplant is rejected. There is in the second. Work in progress shows that second kidneys do not succumb more quickly if they are put into the host as soon as one removes the first."

Medawar [*18*] has recently summarized the evidence which identifies rejection of homografts with an immunological reaction: (1) The existence of a reaction which is similar to the immunologist's secondary response. (In reference to Dempster's communication it should be emphasized that the immunological origin of the second set phenomenon does not necessarily prove that the death of the first graft is due purely to immunological mechanisms); (2) the presence of a phenomenon analogous to the passive transfer of immunity; and (3) experimental proof that reactions against homografts can be prevented by relying on the principle of immunological tolerance (a well known law in orthodox immunological systems).

Role of Cellular Antibodies. The acutal agents of attack on the graft seem not to be conventional circulating antibodies but cells produced by lymph glands. Algire, Weaver and Prehn [*36*] enclosed a homograft in a porous capsule prior to implanting it into a mouse which had been sensitized by an earlier homograft from the same donor. When the pores of the capsule were large enough to allow leukocytes to pass, the recipient mouse destroyed the graft. When the membrane had pores so fine that only fluid but not cells could pass the graft remained intact.

Additional evidence that cells rather than serum are the major factors in the rejection of homotransplants can be found when Mitchison's [*37*] work is examined. He demonstrated that cells taken from lymph nodes draining the area of a tumoral homograft in the mouse and injected into a second mouse of the same inbred strain caused the second mouse to behave as if it had been actively immunized before. This transference of immunity (adoptive) could not be brought about by injecting blood serum of the first mouse into the second but only by a transfer of cells from lymph nodes. Similar results have been reported on skin homografts [*12*].

Role of Humoral Antibodies. The exact nature of the role of the serum as a carrier of antibodies remains indefinite. It appears, however, that the serum may play some part in the rejection of homografts in that homografts will survive in agammaglobulinemic patients [*38*] and skin homotransplants in appropriate strains of mice may lead to the development of antileukocyte antibodies [*39*]. Zotikov [*40,41*] has reported that transplantation of skin leads to the appearance of hemagglutinins among rabbit recipients with the onset of death of the homograft corresponding in time to the discovery of antibodies. He concluded that the failure of some workers to obtain hemagglutinins after transplantation of homologous skin might be due to insufficient graft size, i.e., less than 60 by 100 sq. cm.

In a recent challenging study, Stetson and Demopolous [*42*] postulated that antibody manufactured locally in the graft bed by plasma cells was responsible for the rejection of homografts. They emphasized that the high local concentration of antibody as compared with the amount in the general circulation might explain repeated failures of other investigators to produce the rejection of homografts with passively immunized serum.

Intracellular antibody-like substances however, are the only ones with a firmly established part in the second set phenomenon. The role of the intracellular antibody is supported by the fact that a homograft can survive in a chamber which does not allow the invasion of cells. This chamber may be either the natural anterior chamber of the eye [*43*] or the artifical chamber of Algire [*36*].

Nature of Antigenic Material. What then are the tissue antigens which cause a recipient to reject a homograft? Billingham, Brent and Medawar [*44*] have used ultrasonic vibrations of high amplitude and frequency to split cells into nuclear and cytoplasmic fractions. This technique permits the cells to be broken down without destroying their antigenic power and has produced evidence that the nuclear fraction contains the antigenically active material. As to the nature of this substance, Kandutsch and Reinert-Wenck [*45*] have suggested that the antigen is in the form of a carbohydrate protein complex and Billingham et al. [*46*] have reported that the nuclear antigens are probably similar to blood group mucoids, possibly amino acid polysaccharide complexes. They have described the preparation of a crude, cell-free extract, which is capable of provoking transplantation immunity but not tolerance.

In the present concept of rejection of homo-

grafts the nuclei of grafted cells produce compounds which are similar to blood group mucoids. This material travels via the lymphatics to the regional lymph nodes and there initiates the production of cellular antibodies related to either plasma cells or large "lymphoid cells" [47]. These antibodies in turn travel back to the graft by way of the blood stream and bring about rejection.

Reaction of Graft versus Host. The independent investigations by Dempster [48] and Simonsen [49], showing that a homograft might be capable of reacting against its host's antigens, have been recently re-emphasized by Billingham [50]. He found that in some strain combinations in mice the injection of the newborn with homologous adult splenic cells conferred long lasting tolerance of skin homografts from the donor strains. In these animals, however, a marked involution of lymph nodes was noted in adult life. Even more discomfitting was the observation that in other strain combinations the injected mice either failed to grow up properly ("runt disease"), or died within a week or two of the injection with a widespread involution of lymphoid tissue. A homograft which had been accepted by a tolerant host for more than three months was subsequently rejected when the host was given normal lymphoid cells taken from other members of its own inbred strain [9]. An explanation for this reaction is that the tolerated homograft, despite its appearance, was producing antigens against the host which could not incite a reaction until the host was given normal lymphoid cells. This evidence of a reaction of graft versus host must be borne in mind whenever one considers the possibility of introducing immunologically active cells into human beings.

Autosensitization. The phenomenon of autosensitization has been investigated by Rosenthal et al. [51]. Eighty-nine guinea pigs were injected intracutaneously, intramuscularly and intraperitoneally with autologous skin. Subsequently autografting of skin was carried out. No autosensitization to skin could be demonstrated. This failure may bear some relationship to the phenomenon of tolerance since autoantibodies cannot be formed against substances to which antibody producing cells are exposed during the course of normal development.

Histology of Rejection of Homografts. The histology of the rejection of homografts has been the subject of several studies. One of the best is the report of Darcy [52] who used the submaxillary gland in the rabbit as his test object. Both autografts and homografts were vascularized and apparently healthy on the fourth day. By the eighth day, numerous lymphocytes and plasma cells had invaded the homograft, accompanied by a dilatation and engorgement of blood vessels. On the twelfth day the vessels were for the most part broken down. Destruction of the homograft was complete on the sixteenth day. Autografts progressed normally during this period without pronounced invasion of host cells. The histology of a second set graft revealed that the cellular reaction was confined almost entirely to the graft bed and to the deeper layers of the dermis. Since the graft was not given an opportunity to become vascularized, cellular infiltration of the graft proper did not occur.

Vascular Changes after Transplantation. Edgerton, Peterson and Edgerton [53] have described in great detail the vascular morphology that accompanies skin grafting in mice. The authors used a transparent chamber technique. Their conclusions were as follows: (1) During the period of "take" homografts and autografts show identical initial vascular responses. (2) The establishment of active circulation in any autograft or homograft is largely dependent on the actual end-to-end anastomosis of graft vessels with those of the host and occurs in some cases as early as forty-eight hours after grafting. (3) Rejection of the skin homografts in mice begins on the ninth day (plus or minus twelve hours). The end point of the rejection in the mouse consists of a sudden reduction in the caliber of the larger vessels in the graft accompanied by a slowing of the flow rate in these vessels. (4) The rejection of skin homografts is not accompanied by the development of thrombosis in the vessels of the graft bed unless sepsis is allowed to occur.

The observations of Conway, Sedar and Shannon [54] are in general agreement with Edgerton's description of the vascular morphology.

Genetics of Transplantation of Tissue. Experiments with mice have demonstrated the existence of certain genes or genetic loci which play critical roles in the acceptance or rejection of grafts. The genes playing this role have been named "histocompatibility genes" by Snell. Estimates place the number of loci at not less than fourteen. Incompatibility reactions result

when one or more of the histocompatibility alleles present in the donor is absent in the host [29].

The rules governing the genetics of the rejection of tumoral homografts in mice are known as Snell's Laws [55]. A listing follows: (1) Transplants within a single inbred strain (isotransplants) will grow progressively and kill all hosts. (2) Transplants between strains (homotransplants) do not grow or grow temporarily and then regress. (3) Transplants in F_1 hybrid animals in which one parent was inbred and susceptible grow progressively in all hosts. (4) Transplants originating in an F_1 hybrid animal will grow in all F_1 hybrid animals but not in members of either parent strain.

According to the classic genetic theory of tumoral transplantation, these laws are explained by assuming that a transplant will grow only when a host carries certain dominant genes which were present in the animal in which the tumor originated.

Natural Exceptions to the Rejection of Grafts. Although man is strongly antagonistic to homografts of skin, nature provides at least five exceptions to the concept that skin grafts exchanged between two individuals are invariably destroyed:

First exception: It is well known that monozygotic twins respond as a single individual when tissues are transplanted. Brown's [56] demonstration in 1937 that skin could be exchanged between identical twins forms the basis for transplants of organs between human identical twins. Moreover, when experimental animals such as mice are inbred as litter mates for twenty or so successive generations they develop such a high degree of genetic uniformity as to behave as identical twins with respect to transplantation of tissue. Occasionally, within an inbred strain, however, a failure of the graft is brought about when skin is transferred from male to female. This is believed due to the fact that the male y-linked gene may control or carry specific antigenic substances which bring about rejection of grafts [57].

Peer [58] has studied the behavior of skin grafts exchanged between human parents and their offspring. His results showed that grafts exchanged between fathers and boy or girl infants were rejected before fourteen days but that 25 per cent of the grafts exchanged between mothers and boy or girl infants were long survivals. The grafts, however, were by no means normal skin such as would be found in autografts. The hair follicles and glands had degenerated and the dermis was infiltrated by a dense exudate of lymphocytes. Peer emphasizes that skin grafts should not be interchanged between Rh negative mothers and Rh positive children in cases in which these children had hemolytic disease as newborn infants. The long survival time of certain skin grafts exchanged between mothers and their children is possibly due to an "actively acquired tolerance" caused by an exchange of blood cells between the mother and the developing embryo during pregnancy. It seems evident that whenever possible the mother of a severely burned child should be used as a skin donor rather than the father or friends.

Second exception: Embryos and sometimes neonatal individuals will accept skin homografts [17,59]. Although no studies have been reported in man, there is, at least in chicks, a high incidence of success when skin is homotransplanted at the time of or shortly after hatching. It should be emphasized, however, that the embryonic age during which time animals are not able to recognize alien tissue varies from species to species. For mice the line between immature and adult response is drawn at birth itself [17]. Since the stage of development of a mouse at birth is comparable to a three-month human fetus [17], it would not be expected that humans at birth would possess complete tolerance. Egdahl [23] has recently reviewed the subject of immunological maturation.

Third exception: This was provided when studies by Good and his coworkers showed that skin transplanted from normal to agammaglobulinemic patients would not be rejected [38]. Occasionally, an individual with Hodgkin's disease will react in a similar fashion [60]. The mechanism of this success in transplantation remains obscure despite extensive studies by Good and Varco [61] and Gitlin [62] in attempting to elucidate the immunologic defect. Parenteral administration of gamma globulin to patients who have accepted grafts does not bring about rejection. In any discussion of agammaglobulinemia some reference to the plasma cell should be made. Plasma cells are reduced in those patients with the congenital form of the disease [63]. Plasmocytosis is a characteristic finding in and about the site of

the rejection of homotransplants [42]. These cells may well play a major role in the mechanism of homotransplant rejection.

Fourth exception: In some situations it is possible to exchange skin homografts [64] or even kidneys [65] between non-identical twins. Chimerism has been reported in non-identical human twins [66] as well as cattle; this may form the basis of occasional successful interchanges of grafts between non-identical human twins. To Owen [67] belongs the credit for the first report of natural chimerism. He noted that non-identical cattle twins contain a mixture of each other's red blood corpuscles and postulated that since cattle twins have a synchorial circulation, the fetuses probably exchanged red cell precursors. This natural process in cattle and occasionally in human beings has been artificially produced in the laboratory [68], lending credence to the Burnet theorem [34] that "if a young animal is confronted with an antigen before it is capable of responding by the formation of specific antibodies, then the production of these antibodies in later life will be reduced or wholly suppressed."

Fifth exception: The fifth exception, that of acceptance of embryonic skin by adult recipients, was recently evaluated by Toolan [69] who demonstrated that skin taken from rabbit embryos in the first trimester of pregnancy could be successfully grafted to untreated adult rabbit hosts. These grafts remained deficient in elements of connective tissue even though they remained in good condition. Toolan believes that the ground substance and its possible role in rejection or acceptance of grafts merits the attention of students of transplantation phenomena. Snyderman [70] has applied embryonic skin grafts to patients, concluding that human embryonic skin less than four and a half months of age will survive permanently when transplanted to an adult. There are many deficiencies in Snyderman's criteria of survival. However, the animal experiments by Toolan are well enough controlled to form the basis for this exception.

Prolongation of Graft Survival. What then can be done to prolong the life of homografts? According to Medawar [17] there are three general approaches to the problem: (1) The antigenic propensities of the graft may be altered or "non-antigenic" tissue transplanted. (2) The graft may be transplanted to an area in which it cannot use its antigenic power, i.e., the anterior chamber of the eye, or enclosed in a millipore filter, a "sanctuary." (3) The resistance of the host may be lessened or eliminated.

Alteration of antigenic propensity: In considering the first approach, lessening the antigenic propensity of the graft, Morgan and his coworkers [71] have observed that dehydration-freezing of a tumoral homograft may alter its strain specificity. It has also been shown that an alteration in the homotransplantability of the adrenal tissue of rats will occur on dehydration-freezing [72]. There are three essential differences between homografted adrenals saturated with glycerol and subjected to −80°C. and −190°C. temperatures and those grafted in a fresh state or after storage at −10°C. The former show a diminished lymphocytic response by the host, diminution in the ingrowth of host connective tissue, and a greater regenerative capacity on the part of adrenal cortical cells. An article by Divnogorskaia [73] reports that pregraft preservation of homologous hearts in the frog prolonged survival. Frog hearts were stored at 6°C. for six days prior to transplantation to the chest. Fifteen experiments were recorded. Poor function occurred in four cases; seven hearts maintained viability for over one month and four hearts continued to beat beyond three months.

There are indications that the *in vitro* cultivation of tissues prior to grafting can change the typical mechanism of homograft rejection [74]. However, Gillette and Findley [75] have cultured thirty skin grafts of mice *in vitro* for periods up to sixteen days reporting that all the grafts, both autologous and homologous, exhibited the same sequelae of events after grafting as were seen in freshly transplanted grafts. Although the possibility of altering the antigenicity of a graft is worthy of investigation, if we accept the Medawar concept that the "antigenic makeup of the graft is built into its genetic constitution," then it is difficult to conceive of an alteration of antigenicity without destroying cellular viability.

Granting that embryonic tissues are probably not "non-antigenic" [76], there is a considerable body of experimental evidence which shows that a clinical potential may exist in the homologous transplantation of this type of tissue [11,69,70].

Transplantation of graft to a privileged site: As to the second solution, a graft sanctuary, it is possible to transplant a homograft into a

position in which antigens even if manufactured cannot reach the regional lymph nodes or into a position in which host cellular antibodies cannot reach it. Since the brain has no lymphatic drainage in the ordinary sense, skin transplanted to it will not be able to initiate an immunologic response and consequently will not be rejected [43]. The cornea, however, is a non-vascular structure so that the cells which are the effectors of the host's reaction against homografts cannot get through it unless the cornea becomes vascularized. If vascularization occurs, a graft transplanted to the cornea will usually not take [43]. Greene's [77] observations on vascularization of homografts are at variance with this point. He has shown in guinea pigs that normal adult tissue can be transplanted to the anterior chamber of the eye, become vascularized and persist indefinitely. Greene's work, however, bears out the fact that the anterior chamber of the eye and the brain are the most suitable sites for homologous transplantation. Vascularization, in itself, may not always be associated with graft destruction, but vascularization of the transplanted tissue appears essential before the immune response is capable of producing rejection of the grafted tissue.

The work of Algire et al. has been referred to previously [36]. They have described a series of studies proving that homologous implants contained in millipore chambers will survive almost indefinitely in mice. The filter permits the passage of host nutrient fluids but retains host cells. This, like the anterior chamber of the eye, is a sanctuary. The use of millipore filters presents interesting possibilities for experimental and clinical evaluation.

The lessening or elimination of host resistance: As to the third solution, there are many factors which favorably influence survival time by altering the host's rejection mechanisms. Some of these are innocuous; some are harmful. Some are temporary and some essentially permanent. None provides a solution to the problem of rejection of homografts. A partial list would include: pregnancy, locally administered adrenal hormones, systemically administered adrenal hormones, splenectomy, nitrogen mustard therapy, anticoagulant therapy, desensitization, reduction of serum properdin titers, production of immunological tolerance, chronic uremia, radiation of the total body, reduction of antitryptic titer, antihistaminic drugs, hypophysectomy and/or thyroidectomy, plasmapheresis, pyridoxine deficiency, and extensive burns.

Heslop, Krohn and Sparrow [78] found that homografts transplanted to female rabbits on about the twenty-second day of pregnancy enjoyed a 50 to 100 per cent prolongation of life. This may be the result of enhanced secretion of cortisone-like steroids during pregnancy.

Cortisone administered locally and systemically, in both instances acting through the host [79–81], splenectomy [82,83], nitrogen mustard [83,84], and anticoagulants [85] have all been shown to prolong the survival of skin homografts in experimental animals. Anticoagulants purportedly increased survival by delaying or preventing vascular thrombosis. This explanation may be in error because it has been demonstrated that rejection of skin homografts is not accompanied by the development of thrombosis unless sepsis occurs [53].

Among the experiments reported on desensitization of the recipient prior to homografting of skin are the ones by Allen et al. [86] and Marino and Benaim [87]. Allen demonstrated that the prior injection of rabbits with extracts made from the tissues of their future donors would triple the life expectancy of skin homografts. Marino and Benaim have prolonged the life of skin homografts in rodents by the prior intramuscular injection of donor blood into the recipient.

The term "enhancement," which is a form of desensitization, appears frequently in the literature on tumor transplantation. After the pretreatment of animals, usually mice, with lyophilized material prepared from living homologous tissue, tumors which ordinarily are rejected are then accepted. At this time, why treatment of the host with non-living donor tissue prolongs the life of a subsequent homograft is not known. Snell [29] has proposed that antiserum prevents or delays the antigens of the homograft or at least the effective antigens from reaching the regional lymph nodes. The nodes are thus unable to produce the cellular immune factor which is the major agent in the destruction of the graft. Snell has called this "a walling off" of the graft.

Experimentally, the reduction of the serum properdin levels has produced the acceptance of tumoral homografts in normally resistant hosts [88]. Hubay, Persky and Holden [89,90], however, have shown that there is no pro-

longation of survival of renal homografts when serum properdin levels are reduced.

Immunological tolerance results when immunologically immature animals are exposed to living homologous cells at a stage in development when they cannot produce antibodies. A tissue must be capable of producing transplantation immunity in an adult before it can produce tolerance when innoculated into embryos. Red cells which fail to bring about transplantation immunity in an adult will not cause an embryo to become tolerant [9]. Complete tolerance to homotransplants can be induced in animals by injecting foreign homologous cells into the prospective recipient at a sufficiently early stage of development. This tolerance is specific for tissues from the cell donor [91]. In many species the injection must be made during intrauterine life but in the rat injection shortly after birth suffices [92]. Puzâ and Gombŏs [93] were able to effect immunological tolerance in dogs during the first week of life by a complete exchange of blood. They reported that under these conditions skin homografts survived at least 136 days as compared with eleven days in their control animals. Ashley et al. [94] have described the induction of tolerance by pooled antigens. Blood was pooled from one day old litter mates of rats and reinjected into each animal of the litter. At the end of twenty-one days the skin was cross-homografted among the litter mates. Forty per cent of forty-six animals receiving the pooled antigen had viable homografts at the end of sixty days. Woodruff [95] reports that the intramuscular injection of paternal leukocytes has been employed in two human infants resulting in partial tolerance The father was used as the donor in each case. Leukocyte cream was prepared by centrifuging freshly citrated blood from the father. This was intramuscularly injected into the thigh of the baby at birth. At the age of six months each infant received a split skin graft. Both grafts took perfectly and appeared normal at four weeks. Subsequently both decreased in size but at last report (1957) were viable at seven weeks. In a more recent personal communication to us, Woodruff stated: "I am not at the moment particularly interested in the problem of whether or not tolerance to homografts can safely be induced in human beings. In view of the dangers which have now become apparent, we have abandoned tests on human infants and are going to try to make further tests on animals to try and develop a safe, effective technique." It appears that a state of partial tolerance can be induced in human infants.

The study of the mechanisms involved when tolerance occurs offers to the investigator of transplantation phenomena one of the most fruitful approaches to the problem. Martinez, Aust, Good and Smith [96] recently performed parabiosis between two mice of the same strain. One parabiont being tolerant to a homologous skin graft results in the transfer of tolerance to the normal partner as demonstrated by its acceptance of the same homologous skin. That tolerance is transferable is an exciting finding.

Couch and his associates [97] have evaluated the fate of skin homografts in chronically uremic patients. Serum gamma globulin, serum paper electrophoretic studies, skin tuberculin, isoagglutinin titers, and response to blood group specific substances were within normal limits. Stoloff et al. [98] studied fourteen Shick-negative uremic patients for their capacity to produce diphtheria antitoxin after a booster dose of diphtheria toxoid. Since their response as a group was normal, the authors concluded that the suppression of circulating antibody had little to do with the enhanced survival of homografts in uremic patients.

Sublethal total radiation of the body has been shown to prolong the survival of skin grafts in experimental animals [99,100]. Mice [101] protected against otherwise lethal doses of radiation with homologous marrow are rendered tolerant to skin grafts as well as to hematopoietic tissue of the marrow-donor antigenic type. Not only is homologous skin tolerated but occasionally heterologous, as Zaalberg et al. [102] have demonstrated. These workers protected mice against lethal radiation with rat bone marrow and reported in August 1957 that the skin of donor rats of the same antigenic type as the marrow had survived over fifty-two days.

It has been suggested that since there is a correlation between depression of the antitryptic titer and prolongation of the life of homografts, protease activation may offer an explanation for rejection of homografts [103]. The initial sensitization of the host by a homograft purportedly activates proteolytic enzymes bringing about the death of the transplant. Radiation will depress the antitryptic titer [103].

Foster and Hanrahan [104] have postulated that released histamine might play a role in

homograft destruction. They administered Pyribenzamine® to a Negro woman receiving a split thickness graft from a white man. The graft was apparently viable at the end of sixty days. No follow-up of this case has been found. Other experimental work on the value of antihistaminic agents is at variance [*105*].

A prolongation in survival time of skin transplanted homologously to hypophysectomized, hypothyroid rats has been demonstrated by Schatten and Bergenstal [*106*]. The authors propose that hormonal imbalance alters host resistance.

Chepov [*107*] used a method of total plasmapheresis in dogs with homografts of skin. The plasmapheresis was accompanied by a lavage of the host's blood system, organs, and tissues *in vivo* with a modified Ringer-Locke solution. An increased survival of the skin homograft was demonstrated.

It has been known for over ten years that vitamin B_6 was important in antibody synthesis [*108*]. Fisher and his associates [*109*] have recently demonstrated that when a deficiency of this vitamin is produced by either diet or the administration of desoxypyridoxine, a specific pyridoxine antagonist, a significant increase in the life of experimental skin grafts will occur.

Whether or not extensive burns in themselves are associated with prolonged survival of homografts is debatable. Nevertheless, isolated case reports recording prolongation have appeared in the literature. Kay [*110*] has described his findings in a thirty-five year old man with a 60 per cent burn in whom homologously transplanted skin lasted thirty-two weeks. The donor was a brother aged twenty-seven.

Transplantation of Tumors. This paper will not summarize the massive literature on tumoral transplantation. It should be said, however, that hosts receiving two successive grafts of either normal or neoplastic tissue from the same or genetically related donors usually reject the second more rapidly than the first. In the case of tumors the first implant may grow to a large size before regressing; the second may not grow at all. Billingham [*111*] defined the relationship between transplants of tumor and skin with great clarity when he said: "The main difference between tumor homografts and those of skin is that the former, probably because of their higher intrinsically determined growth rate, once established, appear to be able to withstand a degree of immunological opposition that would prove fatal to a skin homograft. This does not mean, of course, that tumor homografts are necessarily less effective in eliciting transplantation immunity. It means only that their susceptibility is less. As Medawar has pointed out, since tumors seem to need comparatively little encouragement before they will grow in genetically alien soil, they may therefore exaggerate the efficiency of treatments designed to promote their well-being."

"*Tissue Therapy.*" During the past several years many articles have appeared in the Russian literature on transplantation concerning the Filatov concept of tissue therapy [*112*]. Filatov reported that refrigerated corneal transplants would not only function normally but also would bring about the cure of concomittant diseases in his patients. He presented evidence that other tissues such as skin when transplanted after refrigeration had similar beneficial effects on numerous diseases among which was chronic arthritis. Filatov postulated that when a tissue was removed from an organism and left for a period of time at a low temperature, without a protective agent such as glycerol, it produced substances called "biogenic stimulators." These, in turn, purportedly catalyzed normal body reparative processes.

Rogers [*113*] has worked with bovine embryonic skin which was obtained from the intact uteri of freshly slaughtered cows, reporting that this material was useful as a temporary biologic dressing. It survived as long as skin from human cadavers, about ten days, and became well vascularized. From his preliminary studies, he suggests that bovine embryonic skin accelerates healing of wounds in leg ulcers and burns (possibly a form of tissue therapy).

Gueukdjian [*114*] advocates the use of placental extract for trophic ulcers, skin erosion around colostomies, and bed sores. He describes encouraging results in thirty-five patients.

Many investigators in America are unfamiliar with the concept of tissue therapy. A complete bibliography of the subject can be found in *Transplantation Bulletin*, Volume 4, page 165, 1957.

TRANSPLANTATION OF SPECIAL TISSUES

The second part of this review will be devoted to a discussion of some of the currently accepted concepts relating to the grafting of

blood vessels, bone, bone marrow, cartilage, cornea, dura, endocrine tissues, fascia, fat, mucous membrane, nerve, teeth and organs. Since the first section of this article outlined the general principles of transplantation, with particular emphasis on skin, the latter will not be considered again in the comments upon individual groups of tissues in this section. For the present status of transplantation of muscle and tendon, the reader is referred to the excellent book by Peer [*28*].

Blood Vessels. Transplantation of blood vessels is one of the modern developments in the field of tissue grafting which dates to Carrel's early contributions in 1902 [*2*].

The constant search for the ideal prosthesis to replace degenerated or occluded vessels has taxed the ingenuity of the vascular surgeon for many years. Arterial homografts [*115*], arterial heterografts [*116,117*], autogenous vein grafts [*118*], plastic prostheses [*119–121*], autoplastic cutis [*122*], autogenous skin [*123*] and autogenous bowel [*123*] are but a few of the materials used.

De Bakey and Crawford [*115*] have inserted over 800 arterial homografts, studied them histologically for periods up to two and a half years postoperatively, and reported little significant structural change. They believe that although the homograft may be the substitute of choice, the technical and legal factors of procurement, preparation and preservation can only be solved by the development of an ideal prosthetic.

Knox and Begg [*124*] have described two bifurcation arterial homografts in men examined at autopsy eleven and thirty-two months after transplantation. Both grafts showed that all muscle fibers were mummified whereas the elastic tissue was apparently unharmed.

Szilagyi and his coworkers [*125*] have conducted a long term follow-up on 268 cases of arterial disease in which homografts were used. Their conclusions were as follows: (1) Aortoiliac homografts, as judged by clinical criteria, function well up to four years after insertion; however, angiography demonstrates degenerative changes after two years. With the passage of time this degeneration tends to increase in frequency and seriousness. (2) Degenerative changes are much commoner in femoral homografts than in aortic grafts and these tend to appear earlier. Three years after implantation only about one-third of femoral homografts appear to be free from significant structural changes as demonstrated by angiography. (3) From a long range point of view both the human aorta and human femoral artery suffer from serious deficiencies as homologous vascular substitutes.

Both freeze-dried heterografts [*116*] and collagen tubes [*117*] prepared by enzymatic digestion of bovine heterografts have been suggested as arterial substitutes. After observing that the host reaction to freeze-dried homografts appeared more favorable than to fresh homografts, Hufnagel [*116*] experimentally utilized arteries taken from the pig, calf, human being, and lamb transplanted to the dog. All were freeze-dried and sterilized with ethylene oxide. No comparison between the results obtained when long peripheral segments were used as opposed to aortic replacement was made. Hufnagel concluded that pig, calf and human vessels implanted into the dog give results quite comparable to homografts with only "a slightly higher incidence of complications." Collagen tubes prepared by enzymatic digestion of bovine heterografts have functioned as segmental arterial substitutes in the abdominal aortas of dogs for over two years [*117*]. It is the opinion of Rosenberg and his coworkers [*117*] that the results with collagen tubes in the aorta compare favorably to other vascular substitutes.

Autogenous vein grafts have been used to replace peripheral segments of the femoral artery in dogs and man. Recently, Jones and Dale [*118*] have shown in dogs that autogenous vein grafts over a two-year period remain viable without loss of smooth muscle or endothelium. The elastic tissue is decreased but remains as a distinct layer with fibrous infiltration. Jones and Dale recognize that autogenous vein grafts in the aorta are subject to dilation and that aneurysms may develop; however, the authors conclude that aneurysms are less apt to occur in the peripheral system in which the smaller vascular diameter results in a lower tension on the vein wall.

Most students of the subject agree with De Bakey and Crawford [*115*] that the arterial homograft will be replaced by some other material. Edwards [*119*] believes the answer is the chemically treated crimped nylon tube. He recently reported satisfactory results following the implantation of over fifty nylon grafts of

various lengths and sizes and fifteen bifurcation tubes for aneurysms and obstructions. Additionally, Edwards has removed the grafts from the legs of two patients after eighteen and twenty-one months reporting that they showed not the slightest loss of tensile strength. Crawford, De Bakey and Cooley [*120*] have evaluated the clinical use of the synthetic arterial substitutes in 317 patients concluding that knitted dacron was superior to the Edwards-Tapp tube due to fraying of the ends and difficult insertion of the latter.

Another group of investigators, Eiken et al. [*121*], inserted ivalon, grilon, and nylon foil into the abdominal aortas of twenty-five dogs. They stated that ivalon and grilon were well tolerated, but that the moulded non-porous prosthesis (nylon foil) was accompanied by a greater incidence of thrombosis. However, all the longer prostheses of ivalon from the abdominal aorta to the femoral artery became thrombosed within two months. Rob and Chir [*126*] summarize their feelings on plastic substitutes for peripheral vessels by stating that they know of "no plastic implant which works as a satisfactory substitute for the femoral artery of man."

Following a three-year period of major vascular replacement in dogs using nylon, formalin-treated crimped nylon tubes, and autoplastic cutis vascular grafts, Wagner and his associates [*122*] reported that the latter was an ideal blood vessel replacement. Free grafts of dermis seem to have an amazing ability to grow anywhere in the body. It has also been suggested that the cervical esophagus be reconstructed with this material [*127*].

Among the vascular replacements which have not as yet proved satisfactory in experimental animals are autogenous skin (including epidermis) and bowel. Both skin and bowel segments became dilated, thrombosed or sloughed when used as canine aortic replacement. Pratt [*123*] is currently studying peritoneal lined rectus fascia.

Bone. Despite at least 2,000 papers in the general field, great confusion exists concerning the fundamental principles underlying transplantation of bone. For the best recent review of the subject the reader is referred to Chase and Herndon [*128*]. Over 850 references are listed. They cite the fact that the first really scientific approach to the problem was made by Ollier [*129*], who, beginning in 1858 with studies on periostium, concluded that the transplanted periostium remained alive and could become osteogenic under proper circumstances.

Axhausen in 1907 [*130*] and 1909 [*131*] described experiments in which he concluded that the periosteum of autografts would survive and would exhibit osteogenic activity; a few cells of homologous periosteum remained viable after transplantation but heterologous periosteum did not survive. Axhausen's impression was that although transplanted bone itself died, viable periosteal cells were a source of osteogenesis. Some of the present views concerning the fate of autologous, homologous, and heterologous bone grafts in human beings and experimental animals will be discussed herein.

Human autologous bone grafts such as rib, tibia and ileum must be transplanted in juxtaposition to bone in order to survive. When transplanted to fat or muscle the bone is slowly replaced by fibrous tissue over an eight to twelve month period [*132*]. However, membranous bones retain their calcified structure when transferred to areas of soft tissue [*132*]. Although grafts with periosteum obtain an earlier blood supply than those without periosteum, the concensus today is that periosteum is not essential for successful autologous transplantation of bone in contact with bone [*28*]. Simple autogenous onlay grafts tend to diminish in size over a period of time despite the fact that bony union with the host bone remains [*133*]. Peer has noted that bone grafts in contact with bone subjected to stress tend to retain their size. Thus function appears to influence the retention of calcified matrix in a graft. Grafts transplanted to fill skull defects often lose size over a period of time. The idea that function affects bone is sometimes stated as Roux's Law [*28*].

Complete human autologous phalanges with tendons, joint capsules, epiphyseal cartilages, movable joints, and nails have been shown by Peer [*134*] to retain their structure after burial in abdominal fat for periods of at least nineteen months. He suggested the intriguing clinical possibility that amputated phalanges with tendons, joint capsules and nails might be implanted into a patient's abdominal fat and later reattached to the stump as a pedicle using the overlying abdominal skin for a covering.

Peer [*28*] has summarized the behavior of autogenous bone grafts in human beings, concluding that the process of "creeping substitu-

tion" of the graft structure from host bone may not be as active as previously supposed. He presents substantial evidence that the osteocytes in autogenous bone grafts survive as living entities. This is especially true of cancellous rib and iliac bone grafts in contact with bone.

When human homologous bone is transplanted in contact with host bone, the osteocytes die after transfer [*28*]. In preserved grafts they are presumably dead at the time of transplantation [*28*]. Despite this difference fresh and preserved homologous grafts behave similarly when transplanted, the graft structure being replaced in kind by new living bone cells from the host [*28*].

Herndon and Chase [*135,136*] have studied the fate of transplantations of autologous, preserved homologous and fresh homologous knee joints in the dog. Good functional results were obtained uniformly in the autologous transplants. In these, the grafts were rapidly vascularized with the entire graft being reorganized within a period of nine months. In the homologous transplants, regardless of whether the graft was fresh or preserved the initial functional result was good. After a period of four to six months, however, progressive degeneration of the joint appeared with a concomitant limitation of function.

Recently several papers have appeared on the use of anorganic homologous and heterologous bone grafts. The preparation of these grafts by the use of ethylenediamine was described by Williams and Irvine [*137*]. They implanted inorganic bone matrix in dogs and found that it did not produce a tissue reaction. Losee and Hurley [*138*] using the ethylenediamine technique prepared inorganic bone matrix from rats, cows and human beings, and transplanted it to the hind legs of dogs without the reactions usually associated with heterologous transplantation of such tissues. Inorganic bone prepared by ethylenediamine extraction of beef bone and sterilized by autoclaving has been used effectively to fill bony cavities in man without complications. Following a ten-month study, Costich, Avery and Hayward [*139*] concluded "that this agent appeared to fulfill completely the criteria for a suitable material to obliterate bone cavities." Although homologous and possibly anorganic heterologous bone grafts have a place in surgery, autologous bone grafts when available are to be preferred. Healing is certainly more rapid with autologous grafts [*140,141*].

Bone Marrow. The concept of administration of bone marrow to radiated animals was first conceived by Rekers [*142*] who injected bone marrow into dogs after radiation. Dogs which had been exposed to 350 r (L.D. 50) showed only an equivocal improvement in survival. In 1951 Lorenz et al. [*143*] reported that the intravenous administration of homologous bone marrow to mice and guinea pigs exposed to the lethal effects of x-ray radiation increased survival time and promoted recovery. Jacobson [*144*] demonstrated that when mice were given lethal radiation with the spleen shielded, 75 per cent of the animals survived despite the fact that the spleen was removed fifteen minutes after radiation. On the basis of these experiments, he postulated that a "humoral factor" from the spleen aided in recovery.

Many studies have accumulated showing that marrow can be successfully transplanted into radiated animals and that repopulation of the host's depleted marrow cavity does in fact occur. Ford and Hamerton [*145*] used a "chromosome marker" technique and described the fact that homologous marrow administered intravenously to radiated mice appeared in the marrow cavity. Nowell and his associates [*146*] injected bone marrow from normal rats into lethally radiated mice. After four weeks great numbers of alkaline phosphatase granulocytes were found in the mice. (Mature granulocytes of rats are strongly positive for alkaline phosphatase while the same cells of the mouse are negative.)

Although the evidence is convincing that successful transplantation of foreign marrow in rodents will occur subsequent to a lethal dose of radiation to the body or to myelotoxic agents [*147*], the particular role of the spleen or of a concomitant humoral factor in the recovery of marrow is re-emphasized from time to time. Ellinger [*148*] reported that cell-free total splenic extract obtained from heterologous material would protect guinea pigs against a lethal dose of radiation to the body. He had previously shown the protective effect of cell-free saline extracts made from the spleens of normal mice against x-ray induced mortality in this species [*149*]. These observations give support to the concept that a humoral factor from the spleen may play a role in the protection

provided radiated animals by shielding of the spleen. It must be pointed out that the original spleen-shielding experiments of Jacobson [*144*] have not been adequately explained in terms of mechanism of action. Most probably the beneficial effect results both from cellular colonization and a humoral factor or factors.

There is definitely a difference in species in the ability of lethally radiated animals to accept foreign bone marrow. For instance, when one uses the dog to study post-radiation, homologous marrow grafts, failure almost invariably ensues [*150*]. It is known, however, that autologous marrow administered intravenously will protect dogs subjected to 600 r total radiation to the body [*151*]. One of the difficulties in the dog is that radiation in the range of 600 to 900 r (the limit of intestinal tolerance) is not enough to eliminate immune mechanisms and thus permit a successful homologous marrow graft.

Ferrebee et al. [*152*] recently described an experiment in which they used splenectomized male dogs. These animals had had a reduction in lymphoid tissue subsequent to the administration of ACTH. In addition all were subjected to an L.D. 50 of total radiation to the body on each of three successive days. Multiple sublethal doses of x-rays reputedly have more effect on the immune response and less on other tissues than do single doses of radiation [*153*]. Into these splenectomized, male dogs receiving ACTH and repeated sublethal radiation, homologous marrow from a closely related female dog was administered. A successful transplant was recorded using the criterion of the female-type leukocyte in the percentage characteristic of normal females in radiated male dogs. This is impressive evidence but there remains a possibility for error in the microscopic interpretation of the female tag.

The beneficial effect of homologous bone marrow administered intravenously to monkeys is a point of dispute. In a recent personal communication Weston mentions that he has been unable to effect a substantial improvement in survival rate when a 3 kg. monkey is given homologous marrow following 650 r total radiation to the body. Thus far he has studied over 300 monkeys. His results show that heterologous marrow from rats seemed more effective in protecting monkeys from radiation damage than homologous material. Overman [*155*], however, reports that the lethal outcome in radiated monkeys is favorably influenced by homologous marrow. The explanation for this difference in results is not known.

Prior to the institution of radiotherapy in two patients with metastatic malignancy, Kurnick et al. [*154*] collected and preserved autologous bone marrow. This was infused intravenously after radiation. The authors concluded that the infused autologous marrow was innocuous and might have been responsible for the recovery of both patients. Since no marker technique for autologous marrow was used, the mechanism of benefit remains obscure.

Ferrebee [*156*] has given homologous marrow intravenously to six patients. Two of these received bone marrow after chemotherapy for neoplasia, three after total radiation of the body for leukemia, and one without pretreatment with radiation or drugs. A transient "take" was observed in two of the three patients receiving total radiation of the body. When one considers administering a dose of radiation to man capable of altering his immune response so that he will accept homografted tissues, several points must be raised beyond the one question of "take" of the homologous marrow.

First, what is the L.D. 100 for man? This is not known. The L.D. 100 for man has been supposed to be 600 r [*157*]; however, presently available facts are insufficient to either support or contradict the assumption that an acute exposure to 600 r total radiation to the body is the highest one compatible with human survival [*158*].

Secondly, what dose is required in man to destroy the immune response? Here, as possibly in the dog, the limiting factor of gastrointestinal ulcerations which could alone kill despite hematopoietic replacement must be considered. In a quantitative report on the effectiveness of isologous, homologous and heterologous bone marrow, Van Bekkum and Vos [*159*] have demonstrated that the number of cells required to protect the host from acute radiation is related to the degree of antigenic difference between donor and host and that if functional grafts of homologous and heterologous bone marrow are to be obtained in a high percentage of animals, the recipients must have received supralethal doses of total radiation to the body.

Another question which arises when one thinks in terms of massive radiation to humans followed by the administration of homologous

marrow is the reaction of graft versus host. Trentin [*160*] has studied the reaction of homologous marrow against the host, observing a secondary wasting disease without depression of marrow which often results in death following infusions of homologous bone marrow into radiated mice. This "homologous disease" is not seen in mice protected with isologous marrow. There is evidence that the secondary disease may result from an immune reaction of the elements of the transplanted homologous marrow (lymphoid) against the tolerant host. To obviate this reaction of homografted tissue against the host occurring when homologous bone marrow is given to lethally radiated animals, Lengerova [*161*] has administered embryonal blood-forming tissue (liver cells from eighteen to twenty day old mouse fetuses) to mice radiated with 900 r. Protection was demonstrated and in no case did the wasting disease occur.

Studies on the postradiation modification of radiation injury have almost exclusively involved x- or gamma-ray radiation rather than the more densely ionizing radiations such as neutrons. It is known that prophylaxis with Proteus morgani endotoxin [*162*], A.E.T. (S, 2-aminoethylisothiuronium Bromide, HBr) [*163*], M.E.G. (2-mercaptoethylguanidine HBr) [*164*], cysteine [*165*], highly polymerized nucleic acids [*166*], the germ-free state [*167*], and hypothermia [*168*] will protect animals against gamma radiation. However, both chemical prophylaxis with cysteine and the intravenous injection of isologous marrow are relatively ineffective in reducing the thirty-day mortality following fast neutron radiation, possibly because of the greater damage to the intestines [*169*]. Combining antibiotics with isologous marrow will enable 85 per cent of lethally radiated mice to survive fast neutron radiation [*170*].

We are currently investigating the possibility of transplanting tissues between animals with both donor and recipient radiated in states of suspended animation. It has been shown by Hornsey [*168*] that the resistance of adult mice to x-rays is increased by a factor of 2.8 when the body temperature is lowered to 0 to 1°C. The dose which killed 50 per cent of the mice (L.D. 50) at thirty days was 620 r for mice at normal body temperatures and 1760 r for ice-cold mice. No data are available on the immune response of animals withstanding radiation while in a state of suspended animation.

A method which permits autologous bone marrow to proliferate in an ectopic locus has recently been described in this laboratory by Owen and his coworkers [*171*]. In this technique, autologous rib with its contained marrow is inserted into the dog's spleen or omentum. Definite proliferation of marrow occurs after four to six weeks in the splenic and omental sites continuing for at least one year. Since no reliable technic of tissue culture exists to determine the viability of bone marrow, this *in-vivo* culture method may be applicable. Additionally ectopic growth could serve as a marker to determine the exact fate of transplants of autologous bone marrow. Omental implantation possesses clinical promise. Obviously the intravenous route for administration of marrow, depending as it does on the passage of suspended marrow through the minute pulmonary capillaries, may not be optimal.

Cartilage. In 1896 König [*172*] buried segments of autologous rib cartilage to repair partially destroyed cartilage in the larynx and trachea, and in 1899 Von Mangoldt [*173*] successfully transplanted autologous costal cartilage into the nose. A great deal of the pioneer work in the field of transplantation of cartilage thus deals with clinical evaluation. Unfortunately persistence of the cartilage was not demonstrated.

In 1920, Gillies [*174*] reported on the microscopic findings in autografts and homografts of fresh cartilage. His sections eighteen months after implantation showed the cartilage cells to be alive in both the autograft and homograft.

The majority of modern workers believe that both autologous and homologous cartilage will survive transplantation. Peer [*175*] reports viable chondrocytes twenty-seven years after autogenous transplantation of cartilage from the rib, septum and ear. These grafts show little evidence of infiltration by host cells. No new formation of cartilage occurred around the graft although new formation of bone did occur.

As to homologous cartilage, Peer [*176*] has noted that the cartilage cells in fresh human homografts remain viable for long periods of time, over four years. Gibson et al. [*177*] used S^{35} uptake as a test of viability and observed that fresh human homologous cartilage will metabolize S^{35} fifteen months after transplantation. Homografts of cartilage presaturated with glycerol and stored for one month at −79°C.

are dead when examined three weeks after insertion into host animals [178].

Heterologous cartilage has been shown to accelerate wound healing in nutritionally and endocrinologically normal animals. Histologically, wounds treated with cartilage show an increase in reticulum and collagen. Prudden [179] postulates that cartilage may act as a repository for a "repair stimulating fraction."

It is not known why cartilage homografts survive transplantation. It has been suggested that the mucopolysaccharide matrix acts as a barrier against cellular antibodies in a way akin to the Algire capsule [180,181]. Medawar believes that the explanation lies in the avascular nature of the cartilage graft [182].

Cornea. It has been demonstrated that corneal tissue which is known to be dead cannot be transplanted with the expectation of more than an occasional success [183]. On the other side of the ledger a debate still rages as to whether the stromal cells in a fresh homograft persist indefinitely after transplantation or whether they die and are replaced by the stromal cells of the host. Experiments by Maumenee and Kornblueth favor the theory of host replacement [184].

The importance of the sensitivity reaction in opacification of corneal grafts has been demonstrated by Billingham and Boswell [185]. In their experiments a rapid breakdown of homologous corneal epithelium occurred when cornea was transplanted into an animal previously immunized by a skin graft from the same individual.

Clinically and experimentally delayed clouding of clear transplants has been observed. This reaction may be akin to the sloughing of homologous skin transplants. One can reproduce the clouding phenomenon in rabbits by inserting a piece of skin from the same donor which supplied the cornea into the abdominal wall of the recipient. This increases the dose of the antigen. A clouding reaction may take place two or three weeks after the skin has been inserted if the recipient cornea is vascularized up to the graft edge [186].

Although the anterior chamber of the eye is a sanctuary for homologous cornea, when cornea is grafted to the abdominal wall there is a sudden destruction of corneal epithelium two to three weeks after operation. If a second set of corneal grafts or skin from the same donor is then inserted into the abdominal wall of the same recipient, the cornea is destroyed before the eighth day. These observations are of practical clinical value for it is known that 85 to 90 per cent of corneal grafts without blood vessels will remain clear; in homotransplanted corneas with a few vessels only 50 to 65 per cent of the grafts are successful: if the cornea becomes heavily vascularized less than 20 per cent remain transparent [186].

It has been postulated that cornea and cartilage are homotransplantable because the cells are protected by a mucoprotein-like matrix which prevents the entrance of hostile host cells [180]; however, cornea which is transplanted subcutaneously is destroyed as promptly as a skin homograft in the same location [186]. Therefore it is likely that the recipient cell environment with its absence of blood vessels determines the fate of the corneal transplant with the percentage of success varying inversely with corneal vascularity.

Dura. Dural replacement prevents the formation of dense meningocerebral adhesions and the leakage of cerebrospinal fluid. The important criteria for a satisfactory dural substitute are inertness, non-toxicity, and a minimal tendency to form adhesions. Although fascia lata and other autogenous tissues are frequently used today, no ideal substitute has been found.

Crawford [187] recently conducted experimental studies on dogs substituting normal dura with preserved homologous dura. The results he obtained with homologous dural grafts were as good as or superior to those obtained with fascia lata. Crawford's method of preservation was storage of the material in glycerol-oxypolygelatin-potassium citrate at −45°c. Criteria for success included absence of ill effects and no adhesions. Histologic studies were consistent with viability. Crawford concluded that preserved dural homografts could well be the long-sought ideal dural substitute.

In another report on the use of sterilized or freeze-dried homologous dura, Stern [188] reported that a water-tight, tough, pliable replacement for defects up to the size of 96 sq. cm. was successfully accomplished in fifteen of sixteen patients. The author believed that preserved homologous dura was superior to any other type of dural replacement, synthetic or otherwise, currently available.

The papers on the use of dural homografts to fill in dural defects by Crawford and Stern are

impressive studies. Further investigation into the possible use of preserved dural homografts appears warranted.

Endocrine Tissues. There are many studies which indicate that homotransplants of at least some endocrine tissues do not provoke the usual rejection reaction [*189,190*]. Some of the historical highlights and present opinions will be briefly reviewed.

Neuhof [*191*] cites the following early studies: Berthold's demonstration in 1849 of the retention of male characteristics in experimental animals when testicular tissue was autoimplanted, as compared with castrated controls; Schiff's report in 1854 that the striking symptoms subsequent to thyroidectomy in experimental animals were abolished if the gland was removed and then implanted into the abdominal cavity; Lespinasse's observation in 1869 that homologous testicular slices implanted into the abdominal wall and scrotum of a patient who had suffered the accidental loss of both testicles with impotence was associated with a return of potency maintained for two years; Minkowski's conclusion in 1892 that autoimplanted pancreas in animals maintained transient viability; Boinet's systematic studies on the autoimplanted adrenal gland in 1895 in which he demonstrated early death and postulated that autoimplants of the adrenal gland were not likely to succeed because the gland was so closely linked with the nervous system; Dominicis's report in 1897 that adrenal function in animals was lost when the nerve connections to the organ were divided; Knauer's experiments in 1897 on rodents which had undergone ovariectomy in which he autoimplanted ovaries to the parietal peritoneum and into abdominal wall sockets, observing a small number of experiments in which pregnancy subsequently occurred; Cristiani's results in patients recorded in 1905 using histological criteria and noting persistence of parathyroid tissue autoimplanted into muscle over a several years' period.

One of the theories frequently advanced to explain the wide variation in end results when endocrine tissue is autologously or homologously transplanted is Halsted's Law. On the basis of autoimplantation of parathyroid glands in dogs, Halsted in 1909 [*192*] reported that a deficiency must be created before autoimplanted tissue would take and survive. Exceptions to this law were noted by Shambaugh in 1936 [*193*], and Dunphy and Keeley in 1940 [*194*]. The latter described a technique of autotransplantation of the adrenal gland to the ovary of a dog, recording that the number of viable cells in the cortex and medulla is sufficient to maintain the life of the animal indefinitely, and that the autotransplantation can be successfully accomplished without a marked physiologic need for the graft at the time of transplantation. Dempster [*6*] takes issue with Halsted's use of the word transplantation stating that more correctly Halsted implanted endocrine slices of tissues as opposed to transplantation in which an immediate blood supply is provided. Further evidence against the Halsted hypothesis was reported by Braunwald and Hufnagel [*195*]. They found that when the thyroid of a rabbit was autografted, physiologic glandular deficiency was not necessary to establish survival. The weight of more recent experimental evidence appears to be contrary to Halsted's Law.

During the past twenty-five years many clinical attempts to transplant endocrine tissue have been described. Results have not been consistent although occasional successes have been reported. Among the techniques suggested have been adaptation in tissue culture, direct vascular anastomosis, and enclosure of the endocrine tissue in millipore chambers.

In 1933 Stone, Owings and Gey [*196*] reviewed the problem and mentioned adaptation in tissue culture with host serum as a possible solution. More recently Gaillard [*197*] reported the results of transplants of fetal parathyroid tissue after nine to fourteen days' adaptation in tissue culture. Since 1941, thirty-four patients have received such implants. Results were considered successful in seven cases (all in patients under thirty-six years of age) in which improvement lasted for more than a year. In another study of the problem Escamilla and his associates [*198*] implanted living parathyroid tissue into eleven patients with surgical hypoparathyroidism. Fragments of fetal parathyroids 1 mm. or less in diameter were grown in tissue culture and gradually adapted to recipient serum. In one patient the fetal tissue remained functional for nine to ten months; in six other patients transient relief for one to six weeks was experienced. Implants in the remaining four patients produced no improvement.

Results with a different method, that of vascular anastomosis, have been reported by

many investigators. Sterling and Goldsmith [*199*] transplanted the thyroid and parathyroid glands from a still-born infant into the abdominal wall of a patient with long-standing hypoparathyroidism. One year later there were no indications of hypoparathyroidism. I^{131} uptake studies revealed that the transplant was acting like normal thyroid tissue. Sterling [*200*] in his most recent article on the subject of parathyroid-thyroid transplantation in three patients concluded that parathyroid function was present one and a half, two and a half, and five years following homologous transplantation. However, in two of the three patients no evidence of thyroid cell activity could be found. Sterling used dead infants up to twenty-one months of age as donors. Jordan and his associates [*201*] have reported on a patient fourteen months after a thyroid-parathyroid transplant to the groin utilizing a vascular anastomosis. The donor was a still-born infant. In their conclusion the authors stated that the parathyroid glands were probably functioning but the thyroid was not. Although these reports on the transplantation of an entire organ are dramatic and worthy of follow-up, it is difficult to conceive that an individual can support the bulk of an entire organ and not a small free homograft. It is clear that human fetal skin over the age of seventeen weeks *in utero* obtained following miscarriage will be rejected when transplanted to an adult [*202*].

It has been suggested that homologous endocrine tissue might be successfully transplanted if enclosed in millipore chambers. Egdahl, Roller and Varco [*203*] have attempted unsuccessfully to prolong the lives of bilaterally adrenalectomized animals with homografts of adrenal cortex placed into millipore chambers. Brooks, Priaro and De Scoville [*204*], however, conclude from their experiments on rats that homologous adrenal tissue enclosed in a millipore chamber will maintain functional activity. The reason for this difference in results is not known.

It was pointed out at the beginning of this section that endocrine tissue homologously transplanted to experimental animals and human beings occasionally remains for long periods of time prior to being rejected. Woodruff and Boswell [*190*] described the fact that adrenal homografts to the ovaries of rats apparently survived for several months; however, gradual destruction invariably occurred. Although the reason for prolonged survival was not elucidated, Woodruff postulated that perhaps the ovary represented a sanctuary for the adrenal gland. Billingham and Parkes [*189*] implanted homologous ovarian tissue into the subcutaneous region of rodents which had previously undergone oophorectomy reporting a functional survival time of over seventy-seven days. The subcutaneous site of transplantation is certainly not an immunologically privileged one. A possible explanation for the lengthy survival of homotransplanted endocrine tissues lies in the fact that in endocrine tissues the "histocompatibility antigens" are feeble, being capable of eliciting only a weak inmune response if at all [*205*]. Smith and Parkes [*206*] have emphasized with great clarity the fact that the literature on the homologous transplantation of endocrine tissue is filled with reports of successful grafts. They state that "many experimental endocrinologists, blissfully ignorant of immunological complications and with unlimited material at their disposal have made homografts of various tissues, notably mammalian gonads, with complete nonchalance and notable effect. Steinach and Lipschütz, and many others, have grafted ovaries into male animals, testes into female mammals, and both into both, and have made observations on the resulting intersexuality without apparently being surprised that the grafts, essentially homografts, took, persisted, and functioned. Nor can it be supposed that such grafts necessarily broke down after a short while. Lipschütz (1932) for instance, quotes in some detail the case of a castrated male guinea pig which received an ovarian graft, became feminized, and for two years afterwards was used to demonstrate this condition. The graft then turned androgenic, and in its third year after receiving the graft the guinea pig with its male accessory organs in prime condition was used to demonstrate the potential androgenicity of the ovary." It cannot be emphasized too strongly that endocrine tissues frequently do not obey the usual laws of rejection of homotransplants.

Fascia. Many reports have appeared during the past fifty years in which efforts to transplant free grafts of fascia are recorded. One of the first sound contributions to the subject was described by Kirschner in 1909 [*207*]. Realizing that there existed a similarity in structure between fascia and tendon, Kirschner studied the

possible use of this tissue for tendinous defects as well as other purposes. He concluded that autologous fascia would heal in place in a viable state. In 1912 Denk [*208*] observed the histology of a removed, free, autogenous fascial transplant reporting that host fibrous tissue invaded the graft and that fascial grafts were gradually replaced by host tissue. Even today, although most agree that autogenous fascial grafts retain their structure as fascia following transplantation, there is a difference of opinion as to whether the cells in the fascial graft survive or whether host fibroblasts gradually infiltrate the graft replacing the original cells. For a review of this conflict and the history of fascial grafts the reader is referred to the books on transplantation by Neuhof [*191*] and Peer [*28*]. The latter concludes that "the preponderance of opinion favors the viewpoint that free autogenous fascial grafts remain viable after transfer."

In one of the most recent reports on the use of homologous fascial grafts, Schairer and Keeley [*209*] noted, after suggesting that fresh homologous fascia lata could be used to repair diaphragmatic defects in dogs, that after four months the homografts of fascia showed a microscopic structure similar to the original fascia.

In 1946 Chandy [*210*] reported on heterologous fascial grafts implanted into human tissues. He found that four years after implantation the fascia could be grossly identified as fascia. His examination of earlier sections demonstrated an ingrowth of host blood vessels and the presence of exudate host cells within the graft. Chandy's conclusion was that the foreign graft was gradually replaced by host tissue. Peer [*28*] buried homologous fascial grafts in human beings and observed similar findings. However, the experience of Peer with human autogenous fascial grafts buried in fat indicates that fascial cells not only survive but divide.

In contradistinction to the fate of autogenous fascia, the preponderance of opinion is that both homologous and heterologous fascia are replaced by host tissues although they may retain their fascial structure [*28*].

Fat. Peer [*211*] mentions that Neuber in 1893 attempted the first autogenous grafting of fat in human beings. He also quotes that Lexer between 1910 and 1925 reported many successful applications of autogenous grafts of fat.

The fate of fat cells in autologous human transplants is a controversial question. After studying sixty experimental free human grafts of adipose tissue, [*212*] Peer concluded that fat cells would survive autogenous transplantation. He offered as evidence the fact that traumatized grafts of fat lost more weight and volume than gently handled transplants. Thus, the factors that tend to favor cell survival are associated with a larger population of fat cells in the area of transplantation.

Fresh homologous grafts of fat are completely absorbed being replaced by host fibrous tissue [*212*].

Peer [*212*] has reported on the opinions of 187 plastic surgeons to whom questionnaires were sent requesting information on their use of fat grafts. Most surgeons using the free grafts of fat preferred to transplant the adipose tissue with the dermis attached selecting for donor sites the abdominal wall, buttock or thigh. Grafts of dermal adipose tissue appear indicated for reconstruction of the breasts, for hemiatrophy of the face, and for lipodystrophy [*213*].

Mucous Membrane. In 1888 Wölfler [*214*] employed transplantation of mucous membranes in surgery of the urethra. He reported two successful results of homografts placed over raw areas remaining after excision of the strictures. His criteria of success were patency of the urethra in one case and a pale mucous membrane occupying the site of the defect in the other. In the light of our present knowledge it is likely that the end results were the outcome of normal reparative processes rather than viability of homografts.

A study of the literature on transplantation of mucous membranes reveals that interest is largely confined to autogenous material with investigations centering around the phenomenon of bone induction. In 1931 Huggins [*215*] noted that the grafting of autogenous uroepithelium at various locations in dogs resulted in the formation of cysts partially lined with membranous bone which in some instances contained a marrow-like material. More recently Spellman and his collaborators [*216*] reported that autogenous grafts of uroepithelium to the rectus muscle of dogs resulted in the formation of true membranous bone. Bone marrow tissue developed in the cavities of such bone after five months.

Johnson and McMinn [*217*], have evaluated the behavior of autografts and homografts of

transitional epithelium following implantation into the rectus sheath. The behavior is similar up to the fifth day. Epithelized cysts are formed and marked mitotic activity is seen in both the graft epithelium and migrating cells. In autografts the epithelium persists in a healthy state; in homografts after the fifth day, a cellular infiltration with lymphocytes and plasma cells is noted. Epithelial destruction in the homograft occurs during the third or fourth week. Homografts, like autografts, appear capable of inducing formation of bone during the period of their survival.

Marshall and Spellman [*218*] have treated twenty-seven cases of hypospadias by reconstructing the urethra with free autografts of vesical mucosa. When the transitional-celled surface faced so as to come in contact with connective tissue, bone formed in every instance. However, formation of bone was avoided when the transitional-celled surface faced the lumen. The authors appeared well satisfied with the results of urethral reconstruction, reporting that the mucosa remained viable and possessed surprising strength and elasticity.

The feasibility of transplanting vesical mucosa to isolated loops of ileum has been investigated by Jaffe and Persky [*219*]. It was hoped that by this technique some of the disadvantages associated with the use of intact loops would be avoided. A preliminary report mentions three successful transplants as judged by the firm adherence of vesical mucosa to underlying muscularis. Long range studies to determine the presence or absence of secretion, resorption and infection are under way.

Nerve. Usefulness of nerve autografts has been fully established. Nerve homografts are apparently of no value [*220*]. For an excellent bibliography of transplantation of nerves the reader is referred to *Transplantation Bulletin*, volume 1, pages 210–221, 1954.

The problem of inducing orderly regeneration across an irreducible gap in a peripheral nerve has recently been approached with the use of millipore filters [*221*]. Preliminary experiments on animals have demonstrated that this material affords a scaffold for regenerating neural elements. Clinical application of the technique must ultimately wait for the development of a suitable reinforcing matrix. This method for controlled neural regeneration may eventually find application in man as an aid in re-establishing nerve continuity.

Organs. A partial list of the organs which have been transplanted in experimental animals would include the kidney [*222*], liver [*223,224*], lung [*225,226*], heart [*227*], spleen [*228*], pancreas [*229*], and even the entire female breast [*230*]. Ribbert [*230*] demonstrated that the autologous female breast in rodents could be transplanted subcutaneously as well as to the surface of the spleen. Secretion of milk was observed in the transplanted breast when pregnancy occurred several months later.

Among the organs, the kidney has received the most attention. The first report of renal transplantation was written by Ullmann in 1902 [*231*]. He transplanted kidneys between dogs, and from dogs to goats, with only transient success. In 1905 Carrel and Guthrie [*232*] demonstrated that successful autotransplantation of the kidney was possible by means of vascular suture. For a review of the literature of renal transplantation in experimental animals the reader is referred to the article by Hume et al. written in 1955 [*233*]. In general, transplants of autologous kidney placed into the pelvis of dogs will function indefinitely. Homologous transplants in dogs, regardless of location, function an average of about four days and on histological section show acute nephritis with lymphocytic and plasma cell infiltration. Although tubular destruction is marked, the glomeruli appear fairly normal [*234*].

Dempster [*48*] used the kidney to demonstrate that grafted tissue reacts against its host before it in turn succumbs to the reaction of the host. At a variable time following homologous transplantation, a kidney will suddenly become anuric and unless removed will rapidly become necrotic. An arteriogram taken soon after the onset of anuria shows that the renal arteries are in spasm and cortical ischemia is virtually complete. If such a kidney is removed within a few hours of the onset of anuria, often the only pathological change seen is interstitial cell infiltration. There is no obvious histological evidence of what the host reaction has done to the kidney; there is evidence, however, that the homotransplanted kidney has reacted against the serum of the host. The production of immature cells without signs of infection and occurring so rapidly has been interpreted by Dempster as an attempt by the reticuloendothelial system of the kidney to produce antibodies against the serum of the host circulating through it. Immature plasma cells

may indeed produce antibody. If a canine kidney is radiated with 250 r locally twenty-four hours before transplantation, the plasma cell reaction is abolished. The length of survival corresponds to that found in non-radiated transplants. The influence of local radiation on the function of autologous kidney requires further evaluation. It should provide useful information in combating the reaction of graft versus host.

The properdin system, which is an integral part of the natural defense mechanism of blood, has recently been investigated in relation to renal homografts by Hubay, Persky and Holden [*90,91*]. Properdin itself is a beta-euglobulin which is dependent for its action upon complement and magnesium. It is present in normal serum. In this study, zymosan, a carbohydrate derived from yeast cell wall, was used to depress properdin titers. Preliminary experience did not reveal any relationship between the acceptance of renal homografts and the properdin system.

Hume and Egdahl [*235*] in an effort to see if local lymphatics played a role in the destruction of renal homografts, sealed a kidney in a watertight plastic envelope at the time of transplantation. It was thus in contact with the host only through vascular connections. Destruction of the transplant was not altered.

Conway and Griffith [*236*] have shown that an animal which has undergone unilateral nephrectomy can survive and secrete urine when the remaining kidney is nourished only by collateral circulation from a pedicle flap of skin and subcutaneous tissue.

In human beings, permanent survival of the transplanted kidney is possible between identical twins [*237*]. In their most recent report, Murray, Merrill and Harrison [*238*] reported on four successful grafts. The longest follow-up period was three and a half years. One individual sustained by a transplanted kidney from her identical twin successfully completed a normal pregnancy one and a half years after transplantation.

Bricker et al. [*239*] have summarized the functional capacity of denervated, homotransplanted kidneys in identical twins. They concluded that both renal vasoconstriction and vasodilation may occur in the absence of renal nerves; that renal nerves are not necessary for the acute changes in electrolyte excretion occurring after the administration of either diuretic agents or sodium-retaining adrenal steroids; that the renal nerves are not necessary for the chronic regulation of extracellular fluid volume and composition; that renal nerves are not needed to regulate water excretion following intravenously administered Pitressin,® and changes in osmotic pressure.

In their summary of nine cases of homotransplantation of the kidney in human beings, Hume et al. [*233*] reported that transplants which have been anoxic for three to three and a half hours may develop function which is about 25 per cent normal when transplanted; all went through a period of anuria which began either immediately or within twenty-four hours after transplantation; in the four out of the nine transplants which eventually showed some function, the anuria lasted from eight and a half to nineteen days; the general pathological picture was similar to that occurring in experimental animals. The longest homologous survival in this series of nine was five and a half months.

In the light of our present experimental knowledge, one or more of the following conditions must be present to permit the retention and possibly the survival of renal grafts: In human beings, the donor and the recipient must be identical twins or chimeras. Animals must be chimeras or the renal homografts must be first transplanted to the anterior chamber of the eye or the brain and after stromatization transplanted elsewhere in the body. Reciprocal homografts may be exchanged between animals in continuing successful parabiosis [*240*].

Welch [*223*] has developed a technique for the transplantation of an entire liver in dogs, reporting forty-seven transplants with fourteen successes. His criteria for successful transplantation have been two: production of bile by the transplanted liver for at least four days and the survival of the recipient dog for a minimum of five days. In this technique the portal vein and hepatic artery are both reanastomosed to a venous and arterial supply and bile is collected from a cannulized gallbladder. In some instances the liver seemed partially viable up to ten days although it did not secrete bile after four days. The liver is subject to the same type of homotransplantation reaction as is the kidney when transplanted in the dog. Microscopically the changes first seen in the liver are small round cell and mononuclear infiltration of the periportal spaces

which occurs about the fourth day. Thereafter necrosis begins and progresses rapidly, being complete usually by the end of the fifth day. Bile production and bromsulphalein extraction are maximal on the third day after transplantation of the liver. None of the canine livers in this experiment tolerated complete anoxia over thirty-three minutes in spite of antibiotic protection.

Hardin et al. [*225,226*] have demonstrated that the transplantation of an entire lung is technically feasible in the dog. Attempts to prolong the life of lung transplants by blocking the reticuloendothelial system have proved unsuccessful. Benadryl,® cortisone, total radiation of the body and splenectomy have all failed to significantly prolong survival of a transplanted lung as compared with the control group.

Since Mann et al. [*227*] first reported on the transplantation of an intact mammalian heart, over twenty articles on cardiac transplantation have appeared in the literature. Hearts have been transplanted to the neck, groin, peritoneal cavity and chest. In most instances the recipient heart was necessarily left intact to maintain the circulation. Neptune and his coworkers [*241*] transplanted the heart and lungs together in three dogs. Berman and his associates [*242*] have succeeded in maintaining the circulation of a recipient dog with a pump oxygenator while the donor's heart was anastomosed to the free ends of the great vessels bringing about the replacement of a dog's heart in its normal location with the donor heart maintaining the circulation of the recipient dog for periods up to two hours.

When cardiac transplantation is used as a physiologic tool or for the study of the mechanisms of rejection, the transplant is usually placed into the neck utilizing one of two techniques: In the first only the right side of the heart functions. This is accomplished by anastomosing the donor aorta to the distal carotid artery and the pulmonary artery to the recipient's external jugular vein. For a description of the second method, in which all chambers of the grafted heart function, the reader is referred to an article by Luisada and Marcus [*243*].

Sayegh and Creech [*244*] recently reported on thirty-one homologous transplantations of the canine heart. In ten of these the donors were fetuses obtained by hysterotomy, while the remainder were newborn pups. The ascending aorta and pulmonary artery of the graft were anastomosed to the distal common carotid artery and proximal jugular vein of the recipient. Average survival was seventy-three hours for fetal transplants and eighty-one hours for puppy hearts with a maximal survival of ten days.

Lichenstein and Barschak [*229*] have studied pancreatic homotransplantation in dogs and have described a relatively simple technique for vascular grafting. On completion of the anastomosis to the iliac artery and vein of the recipient dog, the pancreas returned to its original color and venous blood could be seen coursing through the portal segment of the transplant into the iliac vein of the host. All animals were sacrificed six to eight weeks after grafting. Histopathologic examination failed to reveal any evidence of surviving pancreatic tissue.

In another approach to the pancreatic problem, Rundles and Swan [*245*] conducted a series of staged operations on dogs aimed at autotransplanting functioning islet cell tissue. The transplanted tissue was transferred to a new location on the anterior abdominal wall and showed evidence in pancreatectomized animals of active function after a latent period of from thirty to fifty-two days. Removal of the autograft after a period of survival without insulin again produced the diabetic state indicating that the graft had been the sole source of insulin.

Sinitsin [*246*] has reported a technique for transplanting the entire head of the frog utilizing an anastomosis between the left arch of the recipient aorta and the arterial cone of the transplanted head and one between the inferior vena cava of the isolated head and the right vena cava of the recipient. The author reported that "at first the grafted head was in a state of postoperative shock but within 5 to 10 minutes the eyes gradually opened. Thirty to 60 minutes postoperatively the head reacted sharply to the touch of skin layers, responding with twitching and contraction of the remaining muscles of the neck and head and with protrusion of the eyes and blinking. The grafted head survived for 48 hours."

Teeth. Dental reimplantation and transplantation date at least as far back as 1593 when Pare [*247*] described a case of reimplantation performed in the following manner:

"Three teeth were loosened and almost torn

out of their sockets. After treatment of the jaw, the teeth were put back in their positions. By this means I enabled him to masticate as formerly with the teeth. I have also heard from a credible person who knew a noble lady that had a tooth extracted from her maid and replanted in the alveolus from which her own tooth had broken out. The tooth became as fast as if it had taken root and she could masticate as well with it as with her own teeth." It can be seen that reports of successful homotransplantation are not new.

Hunter [*248*] was the first investigator to describe in detail studies on transplantation in animals. He mentioned the successful transplantation of human teeth to cocks' combs.

A term which frequently appears in the literature on dental transplantation is "reimplantation" of teeth. Reimplantation describes the procedure of reinserting into the alveolar socket a tooth that has been accidentally extracted or dislodged due to trauma. A review of the literature discloses many and varied accounts of reimplantation with results varying from rapid extrusion to indefinite retention. That the procedure is worthy of clinical trial can be seen from Emmertsen's [*249*] study in which he reported 52 per cent of ninety-two reimplantations viable at the end of three and a half years of observation.

Autogenous transplantation of teeth now appears to have achieved the status of a practical clinical procedure being most commonly employed for replacement of the first molar, held to be the key to the dental arch, by the third molar [*250*]. The optimal time for its transplantation is during the teenage years just after removal of a carious first molar at which time the root of the third molar has started to form but the tooth has still not erupted. The technique and indications for autogenous dental transplantation are described in a report by Hale [*250*].

Homologous transplantation of teeth is generally unsuccessful. Pafford [*251*], however, is experimenting with a homologous tooth bank, inserting the teeth to be preserved into a small plastic vial containing saline benzalkonium chloride, and tetracycline. The containers are stored in a deep-freeze which is maintained at −30°C. When a tooth preserved in this manner is examined after a nine months' period of time, the periodontal tissue exhibits definite degenerative changes although the remainder of the tooth shows good preservation of architectural pattern and cellular detail.

There is a possibility of successful utilization of tooth buds. Shapiro and Johnson [*252*] removed molar tooth buds from the mandibles of young animals aged five to ten days, and transplanted them into the alveolar sockets of young weanling rats aged fourteen to twenty-eight days from which the developing third molar teeth buds had been excised. The animals were sacrificed at intervals varying from one week to two months. Uninjured transplants were shown to grow, differentiate and approach the oral surface. Vascularity of the future pulp became established as the tooth bud grew. The transplantation of embryonic tooth buds offers intriguing possibilities for the future.

PRESERVATION OF TISSUES

There are three general methods of tissue preservation: (1) preservation of viable tissues in a nutrient medium at temperatures above freezing, (2) preservation in a non-viable state by freeze-drying or chemical fixation, and (3) preservation by freezing in either a viable or non-viable state.

Many drawbacks are inherent in the tissue culture method of preserving cells and organs. These include the ever present threat of loss as a result of microbial contamination, the necessity of maintaining a relatively constant temperature, the personnel required for care, and the urgent need to correct rapidly harmful changes in the surrounding medium. Since grafts must frequently be transported, the difficulty in regulating environmental factors is increased. Carrel [*253*] was the first to suggest that arteries for homografting could be preserved in a balanced salt solution at 4 to 6°C., reporting in 1912 that vessels could be preserved in this manner for as long as thirty-five days with little change in the media, only a slight loss of elasticity, and a normal appearance of muscle fibers. Gross et al. [*254*] after exhaustively studying various methods of preserving canine and human homologous arterial grafts found that a balanced salt solution with 10 per cent serum gave the best results. The vessels were found to be histologically viable for as long as thirty-seven days as shown by fibroplastic proliferation in tissue culture [*255*]. Almost all tissues which are transplantable in a fresh state have been transplanted after short periods of preservation in a nutrient medium.

However, the relatively rapid deterioration of grafts preserved by tissue culture in addition to the prodigious efforts needed for satisfactory maintenance lessen the value of the method.

Homostatic tissues such as blood vessels or bone in which viability is not necessary for satisfactory transplantation can be preserved by freeze-drying or chemical fixation. Freeze-drying kills these cells. No evidence at present exists that mammalian cells will withstand chemical fixation or freezing and drying to a residual water content of less than 10 per cent and maintain viability [*256*]. Bone was the first tissue to be successfully freeze-dried for grafts. This was accomplished by Hyatt et al. [*257*] in 1949 and 1950. Marrangoni and Cecchini [*258*] tried freeze-drying and subsequent grafting of arterial segments in dogs with encouraging results in 1951.

An excellent technique for freeze-drying has been developed at the Naval Research Institute. The tissues, such as artery and bone, are aseptically removed and frozen in liquid nitrogen at −196°C. The vapor pressure over the frozen tissues is then reduced to less than 50 μ Hg, so as to sublime the water vapor from the ice without permitting the tissues to thaw. After seventy-two hours of vacuum, the dried grafts are sealed in sterile glass ampules and the tissues stored at room temperature without special care. The freeze-dried tissues are usually reconstituted in saline solution or water prior to grafting. Upper limits of storage time have not been established but arteries and bone have been grafted successfully after two years of "shelf life" [*16*].

Most methods of preservation require the arterial or bone graft to be either removed under sterile precautions or to be sterilized before storage or use. Removing the grafts by an aseptic technique in an autopsy room is difficult at best. In 1951 Meeker and Gross [*259*] reported the sterilization of grafts by high voltage cathode ray radiation. They found that grafts radiated with 2,000,000 to 2,500,000 r equivalent physical units gave satisfactory results except when there had been marked contamination. Chemical methods for sterilization are generally cheap and easy to use, especially beta-propiolactone after the method of Lo Grippo et al. [*260*].

Various chemical fixatives such as formaldehyde, alcohol and glycerin have been used for the preservation of arterial grafts. With alcohol and glycerin the results recorded are for the most part favorable, but the number of investigators using these fixatives is small. It would appear that calcification tends to occur sooner in a higher percentage of formaldehyde-preserved grafts than in those preserved with balanced electrolyte solution [*261*].

Until recently the third technique, that of freezing only, had enjoyed its greatest popularity for the preservation of blood vessels and bone transplants in which cell survival was not essential for functional success. Hufnagel began his work with rapidly frozen arterial grafts in 1944 [*262*], subsequently reporting on the freezing of arterial tissue with either carbon dioxide, ether, or liquid nitrogen and regularly employing a storage temperature of −70°C. Freezing alone is certainly a good method for long term preservation of homostatic tissues, but freeze-drying offers definite advantages from the point of view of convenience of storage for protracted periods.

The discovery by Polge and his coworkers [*263,264*] that glycerol would protect spermatozoa against the previously observed lethal effects of freezing and rewarming has given great impetus to the investigation of freezing for the preservation of tissues in a viable state.

Extensive work by Luyet [*265*] on ultrarapid freezing and the research by Lovelock [*266–268*] on slow freezing have contributed a great deal to the understanding of freezing, freezing injury, and the means for its control.

In any discussion of freezing, difficulties in terminology arise. Smith [*269*] in considering this problem states: "To clinicians, 15°C. is a very low temperature. To inhabitants of the tropics, ice and snow at 0°C. represent severe cold. To a refrigeration engineer −40°C. is a low temperature. Some physicists on the other hand regard temperatures as low only when close to absolute zero. Differences of outlook have similarly led to confusion over rates of cooling. Meteorologists consider a fall in air temperature of 28°C. in eight hours as being rapid. In the meat industry a change in temperature of from 5°C. to −5°C. in 30 minutes is regarded as quick. By contrast, biophysicists of Luyet's school would call the rate of fall rapid only if the temperature changed from 0°C. to −190°C. in a matter of seconds."

Smith has adopted the following classification (Table 1):

TABLE 1

Range of Temperature (c.)	Time	Description
0 to −190°	2 sec. or less	Ultrarapid
0 to −79°	2 sec. to 5 min.	Rapid
0 to −79°	10 min. or more	Slow
20° to any range	1 hr. or more	Very slow

Merryman [270], however, prefers different criteria for slow versus rapid freezing. He refers to slow freezing as a condition under which only extracellular ice crystallization is obtained and rapid freezing as a cooling rate sufficiently high to cause intracellular crystal growth. It is this classification that we will adopt in the succeeding comments.

We have mentioned that when the freezing rate becomes very rapid, ice crystallization is predominantly intracellular. The rates of freezing required are very high, representing a drop in temperature from 0°C. to −190°C. in less than a few seconds [270]. Unlike slow freezing, in which extracellular crystals in themselves are probably mechanically benign, intracellular crystallization can be of major significance especially when the size of the crystal exceeds that of the cell.

Tissues will survive rapid freezing without glycerol if the three requirements of very rapid freezing, storage at low temperature, and very rapid thawing are met [270]. Merryman has demonstrated that red cells can be sprayed onto the surface of liquid nitrogen, rapidly thawed and survive [270]. Since the coolant will not readily penetrate thick slices of tissue, rapid freezing is not practical for the preservation of most types of clinical material. In fact the upper limit for size in the freezing of whole blood is a sphere about 1 mm. in diameter [270].

With the possible exception of skin and human spermatozoa [269] normal mammalian cells must be presaturated with glycerol to survive the ravages of slow freezing and thawing. Presumably glycerol prevents the lethal increase in salt concentration which occurs when ice forms. One mole of glycerin will prevent approximately 3 moles of water from freezing [270].

From a practical standpoint a number of significant accomplishments have been made in the field of preservation of tissues by slow freezing. Spermatozoa [263,264], blood [271], skin [272], bone marrow [273], dura [187], cornea [274], platelets [275], and ovaries [276] have been stored successfully in a viable state by freezing in a medium containing glycerol for many months. In respect to the ovaries, the glycerol method causes a destruction of 90 per cent of the oöcytes [277].

Methods of preserving entire organs by cooling have been studied by Lapchinsky [278]. He has reported that legs and kidneys of dogs preserved at 20°C. to 4°C. for twenty-four hours and perfused by Ringer's solution both before and at the end of preservation can survive permanently after reimplantation and function well.

Although a great deal of success has been recorded concerning the long term preservation of isolated cells and tissues at low temperatures, there exists a formidable gap between this and our ability to preserve an entire organ such as the heart by freezing. Preservation of whole organs by cold is currently under study in this laboratory and equipment has been designed which permits an entire organ to be frozen to within one degree of absolute zero and thawed without gross or microscopic evidence of fragmentation. Since we have been unable to saturate an entire organ such as a heart with glycerol prior to freezing we have adopted a technic of physical dehydration, followed by soaking in 100 per cent glycerol for one hour, to lower the freezing point of an entire heart. Removal of 30 to 40 per cent of the water from a puppy's heart aged one to two months followed by soaking of the dehydrated heart in 100 per cent glycerol for one hour permits the intraventricular temperature to drop to −8°C. without freezing. Puppy hearts will resume intrinsic rhythmicity after at least one hour at −8°C. when transplanted to the neck of a recipient dog.

An extensive literature exists on the attempts to preserve entire animals by cold and the resistance of animals to cooling and freezing. Rats, dogs and monkeys have been revived after respiratory and cardiac arrest following cooling to deep body temperatures only a little above zero. Bats and hamsters have been resuscitated after supercooling to, or partial freezing at, body temperatures below zero. For a comprehensive review of this subject, the report by Smith [279] should be noted.

Polge [280] reported that in the presence of 7.5 to 10 per cent xylose, glucose or sucrose, and

in the absence of salts, bull spermatozoa suspended in egg yolk survived freezing at temperatures down to −40°C.

Parkes [*281*] has envisioned the protection of endocrine tissues during freezing by substances which would volatilize together with ice during high vacuum distillation. Methanol is sufficiently volatile at low temperatures and rat ovaries have survived freezing for several hours in its presence. Future developments may some day permit long term storage of mammalian cells without loss of viability in the dry state at room temperature.

SUMMARY

It is currently accepted that intolerance to homografts belongs in the general category of actively acquired immunity.

Purportedly, when tissues are homotransplanted the nuceli of grafted cells give off compounds similar to the blood group mucoids. It is possible that these antigens are aminoacid polysaccharide complexes. This material enters the lymphatics, travels to the regional lymph nodes, and there initiates the production of cellular antibodies. These in turn reach the graft via the blood stream and bring about rejection of the homograft. Although the intracellular antibody-like substances are the only ones with a firmly established role in the rejection of transplants there is increasing evidence that serum antibodies may also play a part in the mechanism of rejection.

Investigations have shown that a homograft might be capable of reacting against its host. This reaction of graft versus host must be borne in mind when one considers the possibility of introducing immunologically active cells into human beings. Use of embryonic tissue or prior radiation of the graft has been shown to obviate the response of graft versus host.

When skin grafts are rejected, the vascular changes consist of a sudden reduction in the caliber of the larger graft vessels with a slowing down of the rate of flow; however, unless sepsis is present, thrombosis in the vessels of the graft bed does not occur.

A transplant will grow only when the host carries certain dominant genes which were present in the animal from which the tissue originated.

Nature provides at least five exceptions to the concept that skin grafts between individuals are invariably destroyed. (1) Identical twins accept grafts. Inbred animal strains develop such a high degree of genetic uniformity so as to behave as identical twins. (2) Embryos or sometimes neonatal individuals accept grafts. (3) Patients with agammaglobulinemia tolerate homologous skin. (4) Chimeras will not reject grafts. This phenomenon of natural tolerance occurs in cattle twins and has been reported in non-identical human twins. The possibility of tolerance to grafts between a mother and child has been reported. (5) Skin taken from embryos (first trimester of pregnancy) is frequently accepted when grafted to adults. The first and third exceptions have been proved in man.

Knowledge of these natural exceptions to the rejection of grafts exchanged between two individuals may, on occasion, be life saving. On the basis of an extremely close genetic relationship or chimerism, non-identical twins may tolerate grafts exchanged between them. Grafts between a mother and her offspring may not be rejected. Other natural exceptions may also exist. It should not be assumed that all reports of successful grafting are erroneous. We believe that possibly in some cases it is a mistake to credit the success of an interchangeable graft to a specifically utilized therapy rather than to a natural exception.

In general there are three approaches being studied to prolong the life of homografts: (1) altering the antigenic propensity of the graft; (2) transplanting the graft to a privileged site, either the natural anterior chamber of the eye or a millipore chamber with pores too small to allow the passage of cellular antibodies; and (3) eliminating or lessening host resistance.

Probably the third approach offers the greatest promise. Among the procedures and conditions which have been reported to prolong graft survival by acting through the host are included pregnancy, administration of local or systemic adrenal hormones, splenectomy, nitrogen mustard therapy, anticoagulant therapy, desensitization, reduction in serum properdin titers, production of immunologic tolerance, chronic uremia, total radiation of the body, reduction of the antitryptic titer, use of antihistaminic drugs, hypophysectomy and/or thyroidectomy, plasmapheresis, production of pyridoxine deficiency, and extensive burns.

The phenomenon of tissue therapy is discussed. It has been postulated that when tissue which is removed exists in an unfavorable

environment, such as a refrigerator, it produces substances called biogenic stimulators. These supposedly catalyze normal body reparative processes when the tissue is transplanted.

A considerable body of evidence has now accumulated which shows that tumor grafts will survive a degree of immunological opposition sufficient to bring about the demise of a homologous skin graft.

The present status of the following transplantable tissues is discussed:

Blood Vessels. Arterial homografts, arterial heterografts, autogenous vein grafts, plastic materials, autoplastic cutis, autogenous skin and autogenous bowel have been used for vessel replacement. None of these is an ideal vascular prosthesis.

The common denominator determining the histologic fate of aortic and femoral homografts is according to Szilagyi "the intrinsic structural makeup that characterizes elastic and muscular arteries respectively." The connective tissue replacement of arterial homografts is enhanced by a rich complement of biologically inert elastic fibers in the vessel wall and hindered by a high relative proportion of biologically active smooth muscle cells. The longer the follow-up the greater is the degeneration which occurs in aortoiliac and femoral homografts.

Plastics for vascular replacement are being intensively studied but the follow-up period is shorter than has been carried out with homografts so comparisons are difficult to make.

Autogenous vein grafts make satisfactory replacements for peripheral vessels. Although arterial homografts do degenerate over a several-year period and the trend is towards plastics, the latter have not been shown to be functionally superior to homologous artery for the replacement of peripheral vessels. At this writing there is no long range, satisfactory arterial substitute.

Bone. Great confusion still exists concerning the fundamental principles underlying transplantation of bone. Osteocytes in autogenous bone grafts survive as living entities. Osteocytes in homologous bone grafts, transplanted in contact with host bone, die after transfer. In preserved grafts they are presumably dead at the time of transplantation. Both fresh and preserved homologous grafts are replaced in kind by new living bone cells from the host. Human autologous bone grafts such as rib, tibia and ileum must be transplanted in juxtaposition to bone in order to survive. Human membranous bones retain their calcified structure when transferred to areas of soft tissue. Complete human autologous phalanges with tendons, joints and nails will retain their structure after burial in abdominal fat for periods of at least nineteen months. Although grafts with periosteum obtain an earlier blood supply than those without periosteum, the present consensus is that periosteum is not essential for successful autologous transplantation of bone in contact with bone.

Anorganic bone grafts prepared by ethylenediamine extraction of beef bone and sterilized by autoclaving have been used effectively to fill bone defects in patients. Despite the fact that homologous and possibly anorganic heterologous bone grafts have a place in surgery, autologous bone grafts when available are to be preferred. Healing is certainly more rapid with autologous grafts.

Bone Marrow. Transplantation of homologous and heterologous bone marrow can be accomplished in radiated rodents. Less success occurs in the dog and monkey. If functional grafts of homologous bone marrow are to be obtained in a high percentage of animals, the recipients must have received supralethal doses of radiation. Use of embryonal blood-forming tissue is promising. Transplantation of autologous bone marrow administered intravenously is being clinically evaluated. Long term, complication free, transplantation of homologous marrow in human beings has yet to be realized.

Cartilage. Both autologous and homologous cartilage will survive transplantation. Possible explanations for the survival of cartilage homografts include the avascular nature of the graft and the fact that the mucopolysaccharide matrix acts as a barrier against host cellular antibodies.

Cornea. Corneal tissue which is known to be dead cannot be transplanted with the expectation of more than an occasional success. Cells in a fresh corneal homograft are apparently replaced by host stromal cells. Cornea which is transplanted subcutaneously is destroyed as promptly as a skin homograft in the same location. The absence of blood vessels in the anterior chamber appears to permit corneal homotransplants to survive with the percentage of success varying inversely with corneal vascularity.

Dura. Replacing the dura prevents the formation of dense meningocerebral adhesions

and spinal fluid leaks. Autologous fascia lata is satisfactory. Homologous dura may be the best currently available material.

Endocrine Tissues. An impressive group of studies indicates that homotransplants of at least some endocrine tissues do not provoke the usual rejection reaction. One of the theories frequently advanced to explain the wide variation in end results when endocrine tissue is autologously or homologously transplanted is Halsted's Law, which states that a deficiency must be created before transplanted endocrine tissue will take and survive. The weight of recent experimental evidence tends to disprove Halsted's thesis. All reported clinical success in homologously transplanted endocrine tissue, whether it be from a stillborn infant, following adaptation in the recipient's serum, or in millipore chambers, must be measured against the fact that endocrine tissue frequently behaves differently from skin when transplanted, possibly because it has fewer "histocompatibility genes" than skin.

Fascia. Autologous fascial cells remain viable after transfer. Both homologous and heterologous fascia are replaced by host tissues although they retain their fascial structure.

Fat. Recent evidence has been advanced to show that fat cells will survive autologous transplantation. Fresh homologous grafts of fat are completely replaced by host fibrous tissue. Autogenous grafts of fat with the dermis attached appear indicated for reconstruction of the breasts, hemiatrophy of the face and lipodystrophy.

Mucous Membrane. Urethral reconstruction has been accomplished with free autografts of vesical mucosa. When the transitional-celled surface faced the lumen, formation of bone did not occur. In general it can be said that the behavior of homologous and autologous grafts of mucous membrane is similar to skin with the obvious exception that formation of bone does not occur in the latter.

Nerve. The use of millipore chambers to bridge peripheral nerve defects and thus permit an orderly regeneration of neural elements appears promising.

Organs. The kidney, liver, lung, heart, spleen, pancreas, female breast and entire head have been transplanted in experimental animals. Among the organs, the kidney has received the most attention. In general, autologous transplants of kidney placed into the pelvis of dogs will function indefinitely. Homologous transplants regardless of location function an average of about four days. The kidney has been utilized to demonstrate that grafted tissue reacts against its host before it in turn succumbs to the reaction of the host. In human beings permanent survival of transplanted kidney is possible between identical twins. Homologous transplants of kidney occasionally survive for long periods in uremic patients. Large scale clinical usefulness of homologously transplanted organs awaits the solution of the mechanism of homograft rejection.

Teeth. Dental reimplantation describes the procedure of reinserting into the alveolar socket a tooth which has been accidentally extracted or dislodged due to trauma. Over 50 per cent of reimplanted teeth maintain their viability. Autogenous transplantation of teeth is most commonly employed for replacement of the first molar, held to be the key to the dental arch, by the third molar. Success attends the procedure in a high percentage of cases. Homologous transplantation of teeth is usually of no value.

Preservation of Tissues. There are three general methods for tissue preservation: (1) preservation of viability in a nutrient medium at temperatures above freezing; (2) preservation in a non-viable state by freeze-drying or chemical fixation; and (3) preservation by freezing in either a viable or non-viable state.

Almost all tissues which are transplantable in a fresh state have been transplanted after short periods of preservation in a nutrient medium. However, the relatively rapid deterioration of grafts preserved by tissue culture in addition to the strenuous efforts needed for satisfactory maintenance lessen the value of the method.

Homostatic tissues such as blood vessels or bone in which viability is not necessary for satisfactory transplantation can be preserved by freeze-drying. Since freeze-dried homostatic tissues can be stored at room temperature, the technique is to be preferred to preservation of blood vessels and bone by freezing alone.

Freezing represents a potentially practical long term method for preservation of tissues in the living state. Saturation with glycerol will protect isolated cells and tissues against the lethal effects of slow freezing. In slow freezing only extracellular ice crystals form; in rapid

freezing the cooling rate is sufficiently high to cause intracellular growth of crystals. Spermatozoa, blood, skin, bone marrow, dura, cornea, platelets and ovaries, following presaturation with glycerol can be stored in a viable state by freezing.

No review fulfills its function unless the reader finishes with some idea of not only what has been done but what avenues of future research appear to be promising. Homologous transplantation of many tissues is being attempted when, in fact, optimal techniques for the successful autologous transfer of the particular material have not been elucidated. It is our opinion that further investigations in the fields of tolerance, the chemical nature of cellular antigens, and the stromal reaction to transplantation should prove most fruitful. Although the barrier to successful clinical homotransplantation remains high, it is not insurmountable.

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Heart and artery diseases are often associated with extreme overweight. Advanced atherosclerosis is three times more prevalent and coronary artery disease is more common in obese (more than 20 per cent overweight) persons than among those who are underweight. Comparison of persons in the same age group shows that sustained hypertension is twice as frequent among obese persons as among those of normal weight. Other diseases which seem to be more prevalent among overweight persons include anemia, gallbladder disease, diabetes and liver disease. Among persons in the forty-five to fifty year age group, 10 excess pounds increase the chance of death by 8 per cent above normal. Thirty excess pounds increase the chance of death by 28 per cent, and 50 excess pounds, by 56 per cent.

CASE REPORTS

Surgery in the Rocket Era

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TRAUMATIC surgery has progressed by keeping up with injuries peculiar to the various eras in our history. For example, surgery of the hand received its greatest stimulus and scientific advancement with the onset of the machine age. We have now embarked on the era of guided missiles and space travel. This has aroused the imaginations and ingenuity of countless thousands of our youth who envision themselves as scientists of note. Some of these enter engineering schools and channel their dreams down orderly paths adding something to progress. Others choose to by-pass this realistic but often dull experience and begin with the finished product. This has resulted in numerous reports of amateur launchings of home-made rockets in various areas of the country with resultant injuries and fines.

At any rate, occasional new types of major injuries will attend this new fad of the times. We have had one such case which had enough interesting complications to make us believe it worthy of recording in the surgical literature. We propose to present this case briefly in outline form and then enlarge on its important aspects in our comments.

CASE REPORT

A. L., a twenty-four year old man who had an illustrious school record in engineering, was firing a home-made rocket with some associates in a park on the northern outskirts of Omaha, Nebraska on the afternoon of February 8, 1958. On the second attempt at launching, the rocket made a faulty take-off, traveling across ground an estimated 80 yards where it struck its designer in the lower left side of the abdomen, the pointed end passing completely through his body. His companions loaded him into the back seat of a car and drove him to the Emergency Room of the Immanuel Hospital.

At this time the patient was found to be conscious, in severe pain, but not in shock.

Preparation of the patient for surgery was as follows: The patient was given morphine sulfate, ¼ gr., one-half intramuscularly, one-half intravenously, to combat his excruciating pain. An intravenous drip of 5 per cent dextrose in water was started and five units of whole blood were readied for him. He was then taken to the operating room.

In the operating room his clothing was removed disclosing the rocket ends protruding from both sides of his body. (Fig. 1.) A Foley catheter was inserted and clear urine was obtained. This indicated to us that the bladder was probably not traumatized.

The patient was positioned in the left decubitus position and a general anesthetic administered with oral-tracheal intubation. His skin was prepared

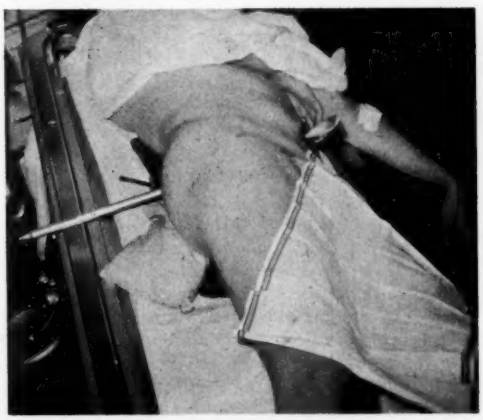

FIG. 1. Photograph showing rocket through the patient's abdomen.

FIG. 2. Photograph of patient five months after his injury. The rocket pictured is the one that had impaled him.

with a soap and water scrub and tinted zephiran solution. The posteriorly protruding front end of the rocket was cleansed with iodine and alcohol.

The initial operative procedure was as follows: A transverse incision was made extending from near the entrance wound to the right iliac crest and the peritoneal cavity was entered. The rocket was exposed as well as possible to determine what vital structures it approximated or perforated. This was difficult as a great deal of the terminal small bowel was wrapped around the rocket. The rocket was then pulled out by the fins. It measured 28 inches in length and ¾ inch in diameter. Immediate massive hemorrhage into the peritoneal cavity ensued. After a quick search the source was located in the right common iliac vein and both ends of the vein were doubly ligated. Blood loss was combated by blood transfusions with the addition of 10 ml. of 10 per cent calcium gluconate. Blood in the amount of 4,500 cc. was given.

Exploration was then carried out. Clothing in the entrance wound was found to extend into the peritoneal cavity. There was a third degree burn of the entrance site extending down to the musculature of the abdominal wall. In addition, there were severe burns of all the intra-abdominal structures with which the rocket had come in contact, including portions of the terminal ileum, the mesentery of the small bowel, the omentum, the right hypogastric artery and the right ureter. Several loops of the terminal ileum were perforated and there was a hole in the bony pelvis in the region of the right sacroiliac joint.

Surgical repair consisted of resection of 7 feet of terminal ileum, along with the cecum, and construction of an end-to-end enteroascending colostomy with interrupted sutures; repair of all omental and mesenteric defects to prevent internal herniations of the small bowel; reperitonealization of all raw surfaces; and the use of multiple drains before closing the incision.

Postoperatively, the patient was kept on nasogastric suction and parenterally administered fluids for four days. He was given Combiotic® ampules twice daily intramuscularly for six days and 500 mg. of Terramycin® intravenously twice daily for four days. Three thousand units of tetanus antitoxin was given immediately postoperatively. Because of a low hematocrit, more blood was also given. Dressings were changed periodically beginning on the fifth postoperative day and the drains slowly advanced until they were completely removed on the tenth postoperative day.

The postoperative complications were as follows: On the sixth postoperative day, in spite of the antibiotic therapy a furuncle developed on the index finger of the patient's left hand which had to be incised and drained.

On the eighth postoperative day clear alkaline drainage with an odor of ammonia and thought to be urine, appeared from the posterior wound. An intravenous urogram was performed several days later showing good function in both kidneys. The left ureter was visualized in its entirety but the distal end of the right ureter could not be seen. A retrograde urogram was then taken on February 24, 1958. The ureteral catheter could only be inserted up the right ureter a distance of 14 cm. Radio-opaque dye injected through the ureteral catheter promptly appeared at the posterior exit wound site, proving the presence of a ureteral fistula on the right. Right nephrectomy was advised.

The patient was unable to walk and had a foot drop on the right side with some ankle edema and causalgia-type pain. X-ray films showed a fracture through the right sacroiliac joint.

On February 26, 1958 the seventeenth postoperative day, bright red blood began spurting out of the exit wound posteriorly and the patient went into shock. The wound was tightly packed with a gauze roller, and the patient taken to surgery.

At the secondary surgical procedure, after the usual skin preparation and draping, a long right paramedian incision was made. The bleeding was found to be coming from a large defect in the right hypogastric artery. Both ends of the artery were doubly ligated with heavy black silk sutures. The right external iliac artery had the exact appearance of far advanced arteriosclerosis, but it was patent and intact.

A segment of the right ureter about 3 inches in length was found to have been completely broken down so right nephrectomy and ureterectomy were performed. Bleeding was excessive and the patient received a total of 17 pints of blood (8,500 cc.), with calcium gluconate again added, during the procedure.

Postoperatively, because of a low hematocrit and hemoglobin more blood transfusions were administered until the hemoglobin rose to 13 gm. per cent and the hematocrit to 38 per cent. In spite of this the patient maintained a persistent tachycardia and healthy granulating tissue failed to develop in the entrance and exit wounds. Depleted blood volume was suspected and therefore a blood volume study was carried out. This confirmed our suspicions, so more blood was given until the blood volume returned to near normal. At this point the patient's pulse rate returned to normal and the wounds showed signs of healing.

The patient was given a pair of crutches and became ambulatory with a foot drop brace.

He was discharged from the hospital March 29, 1958, seven weeks after admission and following transfusion of 36 pints (18,000 cc.) of blood—nearly three exchange transfusions. His foot drop persists, but in all other respects he is leading a normal life. A recent photograph of the patient, with his rocket, is shown in Figure 2.

COMMENTS

This case presents a number of interesting problems, preventable and otherwise, which will be commented upon separately.

The Removal of Impaling Missiles. Not yielding to temptation is sometimes wise. In this case it was life-saving. A patient in severe pain with a 1 inch in diameter steel rod impaling him, who is not in shock and obviously not bleeding internally or externally can create a sense of horror and pity in those with him whether professional personnel or laity. The oft heard remark is "Why doesn't someone pull that rod out of him?", and then, "Here is the doctor—he will pull it out." This creates an interesting situation with an impulsive temptation to carry out this ill-fated plan. At this point the only sensible temptations to yield to are the clearing of the room of all unnecessary personnel and reminding the ones remaining of their status in a surgical team. Soon it will become obvious that a strong anodyne given intravenously followed as soon as possible by a general anesthetic will control the patient's pain and still do nothing to alter his internal injuries. The appropriate body cavity can then be surgically violated so that the steel rod can be withdrawn safely under direct vision and any sudden hemorrhage can be controlled. In this case the missile had perforated the right common iliac vein but its presence acted as a tamponade. As soon as the missile was withdrawn massive hemorrhage resulted which would surely have been fatal unless quickly controlled.

Control of Infection. Marauding armies of pathologic microorganisms following brilliantly inspired surgical procedures, have resulted in the appearance of wide expanses of skin showing through halos of thinning hair on many a surgeon's head. Rigid aseptic technique, adequate drainage, appropriate use of antibiotics, and the use of tetanus antitoxin when indicated, can still prevent many serious, and often lethal infections postoperatively. In this case it is believed that, although a real effort was made to adhere to all of these principles, the major factor responsible for the prevention of a serious postoperative infection was adequate drainage of all traumatized areas.

Adequate Blood Replacement. Perilously low blood volumes produce shock which, if prolonged, can produce fatal renal function changes. Less severe blood volume deficiencies prevent healing of wounds, delay convalescence and often lead to such serious complicating factors as coronary occlusions and thrombophlebitis. For these reasons adequate blood replacement is mandatory in the severely injured patient. Blood volume studies are of great help.

Prevention of Transfusion Reactions. Citrated blood has a low pH, low oxygen concentration, low calcium content and high potassium content (calculated at 15 mEq./L. for twelve day old blood and 20 mEq./L. for twenty day old blood). With multiple transfusions citrate intoxication is common primarily due to hypocalcemia but also to hyperkalemia. The addition of calcium gluconate prevents symptomatic hypocalcemia and also acts as an autogonist to the potassium ion in the blood. We believe this is an important adjunct to multiple transfusions such as that given this patient.

Secondary Complications. The primary concern in this particular type injury is the late sequaelae of the burns of vital internal structures. In this case there was an obvious burn of the right ureter and the right hypogastric

artery. Not knowing the status of the function of this man's kidneys, it did not seem wise to tie off this ureter which was perfectly intact, at the time of his initial surgery. It was thought by the surgeon (J. B. D.) that external drainage was adequate to prevent peritonitis in case the burned ureter should undergo necrosis. In retrospect, however, it would have been wiser to ligate the burned hypogastric artery at the time of the initial surgery than to take a chance on its maintenance of viability and continuity. In this case failure to do so nearly resulted in a fatal delayed hemorrhage. It is interesting to us that the diseased artery did not perforate until seventeen days after its injury. Perhaps it would not have broken down from the burn had it not also been bathed in urine from the damaged ureter.

It will be interesting to discover the ultimate fate of the right external iliac artery. Will it return to normal, or will a replacement graft be necessary in the future?

The four horsemen among the communicable diseases of childhood are measles, scarlet fever, whooping cough and diphtheria. At least, they used to be the most dangerous. Thanks to medical science and new drugs, however, most of their sting is gone. The death rate among children from these four diseases, The Health News Institute reminds us, declined 99 per cent between 1910 and 1956.

Intradiaphragmatic Cyst

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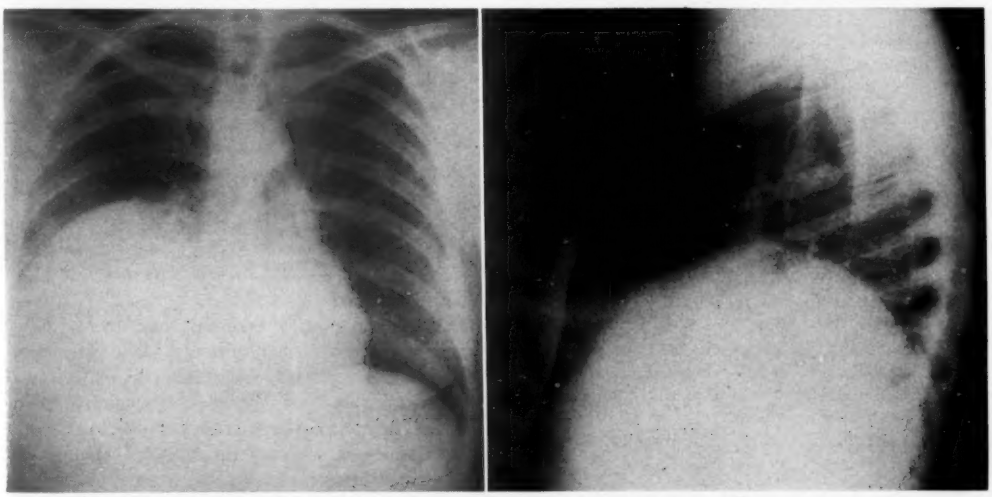
CYSTS lying within the muscle of the diaphragm are rare. In a review of recent surgical literature Kesseler and Maier found only seven such cases, to which they added another [4]. A ninth case has since been reported by Buddington [1]. Several other cysts have been described as being near or attached to the muscle of the diaphragm without actually traversing it. This group will not be discussed herein.

The previously reported intradiaphragmatic cysts are of three general types: bronchogenic, mesothelial and cysts of uncertain origin that are characterized by a fibrous wall. Three of each type have been described. To these is added another case of a fibrous-walled cyst which I believe is the largest intradiaphragmatic cyst that has been recorded.

CASE REPORT

B. H., a thirty-six year old white female physical education instructor, was admitted to University Hospital for the first time because of pain in the right upper quadrant of the abdomen of five days' duration. The pain had at times radiated to the inferior angle of the right scapula. There had been some nausea but no vomiting.

Physical findings on admission were moderate tenderness in the right upper quadrant, without palpable masses or viscera, and percussion dullness over the base of the right lung field. Her initial white blood cell count was 8,600 per cu. mm., with a normal differential. The pain subsided in about forty-eight hours. A gallbaldder series and an upper gastrointestinal series then were performed. Admission x-ray film of the chest and fluoroscopy demonstrated a high fixed diaphragm on the right. (Fig. 1A and B.) The cholecystogram showed a normally functioning gallbladder with no evidence of calculi. The position of the gallbladder was normal. These findings were interpreted as either an



1A 1B

FIG. 1A and B. Admission x-ray films of the chest demonstrating the smooth, elevated right diaphragm. Fluoroscopy proved it to be fixed.

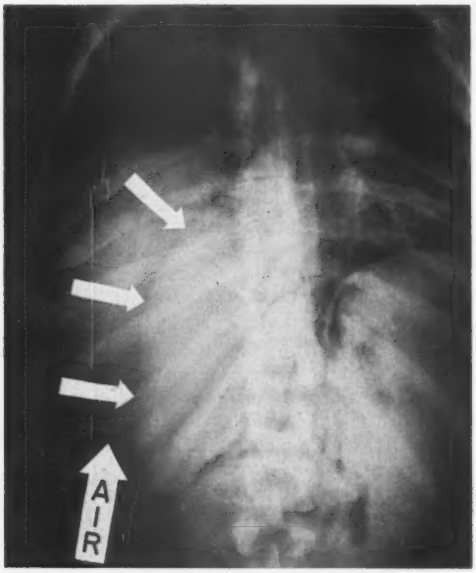


FIG. 2. Diagnostic pneumoperitoneum. The air column shows the liver to be displaced inferiorly and to the left (arrows). The cyst is seen in the area under the right diaphragm normally occupied by the liver.

infrapulmonary fluid collection or marked relaxation of the right diaphragm.

It was found that the patient was known to have had a high right diaphragm for over twenty years. Six years before admission she was turned down in an Army examination; she was told she had a cyst of the liver. A survey chest film taken one year before admission showed the high fixed diaphragm. In spite of the long duration of this finding, no symptoms in any way could be referred to it. She had always been very active in her work as a physical education teacher.

A complete liver profile was essentially normal. An air contrast study of the peritoneal cavity was carried out by inserting air into the peritoneum and taking multiple views. (Fig. 2.) In this way it was found that the liver was displaced inferiorly and to the left by a soft tissue mass under the right diaphragm. This seemed to be separate from the liver surface.

The possibility of a pedicle attachment to the liver could not be ruled out. The clincial diagnosis of probable amebic cyst of the liver was made. Several stool cultures were negative. Since the patient's symptoms had subsided, surgery was not indicated. She was discharged on the seventh hospital day.

She was readmitted nineteen days later with a recurrence of the pain in the right upper quadrant. Now it was also referred to the right shoulder. In a short time she was taken to surgery. A transpleural approach was selected. The right eighth rib was resected and the pleural space was entered through the incised rib bed. The cyst was seen immediately; it appeared to have the size, shape and tension of a standard football. (Fig. 3.)

The overlying lung was slightly atelectatic from pressure. The cyst wall was separated from the parietal pleura by a few muscle fibers. (Fig. 4.) The middle and lateral thirds of the diaphragm had attenuated and most of the fibers had been thrown to one side.

Dissection at first was difficult due to the size of the cyst. It was inadvertently ruptured and released 1,500 cc. of milky appearing fluid. This did not have the consistency of chyle and there was no odor. The cyst was unilocular and the wall was very thin. It was then removed from its bed by blunt and sharp dissection. This was necessary only where the cyst attached to the tendinous portion of the diaphragm. There was no attachment to any other tissues such as the right kidney or suprarenal gland. It did not enter the peritoneum. In staying close to the cyst wall no major vessels were encountered. The lowest pole of the lesion extended to the level of the third lumbar vertebra. After its complete removal the diaphragm was plicated with silk. A large portion of the attenuated muscle was excised. This put the diaphragm at about its normal level. Lung expansion was excellent with pressure by the anesthetist. A thoracotomy tube was placed in the ninth posterior interspace; a cigarette drain was placed in the subdiaphragmatic extraperitoneal space and was brought out through a separate stab wound. The postoperative course was uneventful and the patient was discharged on the eighth postoperative day.

Pathologic examination showed that the cyst wall was thin, soft and white in color with several muscle fibers adhering to its outer surface. The microscope showed it had a fibrous wall. (Fig. 5.) The cyst fluid was free of bacteria; it contained no free fat. The following chemical values were obtained: cholesterol, 357 mg. per cent; chloride, 573 mg. per cent; sugar, 11 mg. per cent; total protein, 8.4 gm. per cent; albumin, 5.8 gm. per cent; and globulin, 2.6 gm. per cent.

COMMENTS

Mesothelial and bronchogenic cysts of the diaphragm are thought to be congenital. Mesothelial cysts result from malformation of the diaphragm by the pleuroperitoneal membrane and the septum transversum. An invagination of the advancing edge of the pleuroperitoneal membrane prior to its fusion with the septum creates a potential cyst cavity [3]. Mesothelial cysts of the pleura or pericardium or pleuropericardial cysts result when a similar

FIG. 3. Surgical approach through the bed of the resected eighth rib. The cyst bulges markedly into the thorax compressing the lung superiorly.

FIG. 4. The cyst has been partially decompressed. The pleura is elevated and some fibers of diaphragmatic muscle are seen on its undersurface.

invagination involves the pleuropericardial membrane and the septum transversum. Bronchogenic cysts are thought to have their origin in the pinching off of a nest of cells from the main mass of pulmonary tissue by the advancing edges of the membranes and septum that fuse to form the diaphragm. The location of the cyst, whether it be in the thorax, abdomen or diaphragm, depends upon the element pinching off the cells [*5,6*].

The etiology of fibrous-walled cysts is uncertain because they lack a characteristic lining. One theory is that they are the result of an inflammatory process [*7*]. Another theory suggests they originate as mesothelial or bronchogenic lesions and that the lining loses its cellular characteristics due to chronic inflammation within the cyst.

The diagnosis of intradiaphragmatic cysts is difficult because of the lack of pathognomonic features. Of the ten reported cases, five were essentially asymptomatic. They were found because of survey x-rays. The other five had various symptoms including cough, dyspnea, back pain and abdominal pain. There were no consistent physical findings. The diagnosis can only be made on the basis of x-ray or surgery, or both. The present case illustrates the value of pneumoperitoneum in the diagnosis of lesions in this area.

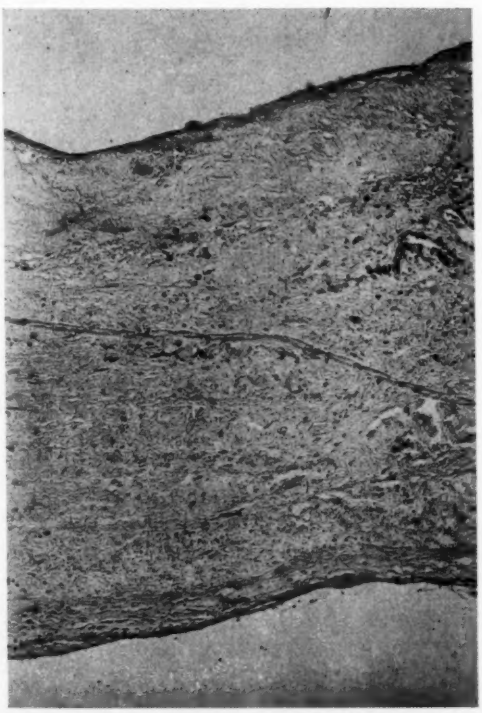


FIG. 5. Microscopic section of cyst wall. There is no lining epithelium. The wall consists of fibrous tissue.

The treatment of intradiaphragmatic cysts or of any lesion suspected of being a diaphragmatic tumor is surgical exploration. The uncertainty of the diagnosis and the fact that most diaphragmatic lesions are malignant supports this approach [2]. There have been no reports of malignant cysts, but lesions thought to be cysts have later proved to be solid malignancies. For this reason early exploration is the treatment of choice.

SUMMARY

A case of intradiaphragmatic cyst is presented. The etiology of the various types of these cysts is reviewed. The difficulty in diagnosis and the value of pneumoperitoneum is briefly discussed. Surgery is recommended as the treatment of choice.

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Familial tendencies play a role in obesity (a condition in which weight is 20 per cent or more above normal). When both parents are of normal weight, only 10 per cent of the offspring can be expected to be overweight. When one parent is obese and one is of normal weight, however, 50 per cent of the offspring may be overweight. If both parents are obese, 80 per cent of offspring may be overweight. "The overweight state is influenced apparently not only by environment but also by genetic factors. Studies of identical and of fraternal twins indicate that food habits are not the main factor in obesity in families," *Patterns* reports (Parke Davis & Company).

Hyponatremia Due to a Villous Adenoma of the Rectosigmoid

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THE problem of the villous adenoma of the colon has been well reviewed within recent years [1]. The subject of hyponatremia has likewise been adequately treated in the literature [2]. However, the occurrence of a case of hyponatremia secondary to a villous adenoma has not been recorded. It is the purpose of this report to present the case of a sixty-three year old white man with such a problem.

THE ELECTROLYTE SODIUM [2]

Sodium is largely responsible for the maintenance of the osmotic pressure of, and the regulation of the volume of, the extracellular fluid compartment. This ion is present in every body secretion. This determines the distribution of the body water. Any loss of the sodium content of the body is under control of the adrenal cortex, the pituitary and the kidney. In surgical disease, there may be abnormal losses from vomiting, diarrhea, excess sweating and also from excretion in response to developing water deficits. In this latter state, the following sequence of events takes place: first the body excretes a small amount of sodium, drawing water along with it; the kidney begins to conserve sodium ion, and the sodium ion disappears from the urine; at the same time, the sodium ion concentration rises in the extracellular fluid compartment; this draws water from the intracellular fluid compartment; clinically, this produces severe dehydration; the patient may show renal failure, mental confusion and muscular weakness. The patient may also exhibit a fall in blood pressure, nausea and vertigo. There is a reduced renal blood flow and glomerular filtration rate, thus producing delayed excretion of water and salts.

If the sodium ion concentration is above normal levels (hypertonicity), the osmoreceptor–posterior pituitary axis is stimulated to secrete an antidiuretic hormone. This in turn, produces retention of water.

If the sodium ion concentration is below normal levels (hypotonicity), the secretion of the antidiuretic hormone is inhibited and diuresis results. Elevated sodium ion concentration will increase neuromuscular irritability and will also produce edema.

The normal adult is in sodium balance and will excrete as much as he takes in. When the sodium intake is zero, excretion of sodium ion is appreciable for two days but then becomes negligible. This is an indication of the loss of extracellular fluid. Table 1 presents a summary of the features of hyponatremia.

THE VILLOUS ADENOMA

A villous adenoma is a specific type of adenoma in the colon [1]. According to Wheat and Ackerman [3] and Hines et al. [4], the colonic villous adenoma is usually a broad, flat, sessile tumor whose surface is velvety and glistening in appearance. Microscopically, the villous character is seen to be due to innumerable tiny, finger-like projections of loose supporting vascular stroma, covered by a single layer of columnar epithelial cells. Prior to 1948 [5], these tumors were not treated as a separate entity but were grouped in the various categories of benign and malignant papillomas, polypi and adenomas.

These adenomas usually occur in the older patient whose average age is sixty years. There does not seem to be any sex predilection. Hines et al. [4] found that this type of polyp made up 1.85 per cent of their group of 2,000 polyps.

The villous adenomas are found predominantly on the left side of the large bowel. In

TABLE I
HYPONATREMIA [2]

Causes	Symptoms	Treatment
Postoperative overhydration	Weakness	Prevention since frequently irreversible and fatal
Administration of excess water	Apathy	Sodium bicarbonate
Vomiting (excess)	Lassitude	Sodium lactate
Water deficits (early)	Giddiness	Hypertonic sodium chloride
Gastric suction (prolonged)	Headache	Serum albumin
Diarrhea	Subcutaneous dehydration	
Salt-losing diseases (renal, pulmonary, cerebral)	Anorexia	
	Nausea	
Heat exhaustion	Vomiting	
Excessive sweating	Abdominal cramps	
Congestive heart failure	Weight loss	
Malnutrition	Oliguria	
Nephrosis	Paralytic ileus	
Cirrhosis	Azotemia	
Hypoalbuminemic states	Confusion	
Hypoadrenalism	Delusions	
Biliary drainage	Psychoneuroses	
Pancreatic drainage	Hypotension	
Intestinal suction	Peripheral circulatory failure	
	Death	

one series of fifty cases, 79 per cent were in the rectosigmoid or distal to that point [3]. Most of these tumors will then be palpable on rectal examination or visible on sigmoidoscopic examination. A barium enema with air contrast study should demonstrate the remainder.

In thirteen (26 per cent) of fifty cases of villous adenoma [3] in one series, and in ten (27 per cent) of thirty-seven in another [4] there was evidence of malignant change. Biopsies may reveal the diagnosis of villous adenoma but there is a 25 per cent chance that the malignant zone of the tumor will be missed on biopsy [3]. In approximately one-third of the cases another tumor, usually of the bowel, either benign or malignant, is present [3].

The size of the villous adenoma varies tremendously (0.5 to 20 cm. [3]) and is of no aid in predicting the presence or absence of malignancy.

SYMPTOMATOLOGY

The presenting symptomatology of the patient with a villous adenoma of the colon is: (1) the passage of large amounts of mucus which when mixed with stool may mistakenly be called diarrhea; (2) the passage of frequent watery stools; (3) the passage of blood per rectum which may rarely be massive in amount; (4) the feeling of incomplete evacuation; (5) if low in the rectum—tenesmus, fullness, desire to defecate; (6) occasional prolapse of the tumor through the anus; (7) intussusception of the tumor with symptoms of intestinal obstruction; and (8) occasional passage of fragments of tumor per rectum.

The treatment of the benign villous adenoma is adequate local excision with the removal of a margin of normal tissue, all in one piece. The treatment of the preoperatively diagnosed malignant villous adenoma should be the same radical treatment reserved for any malignancy discovered in that particular location and type of patient. The villous adenoma which is completely excised, and then on microscopic examination of multiple sections is found to be malignant, should be reoperated upon and treated as one would treat any malignant lesion of the bowel in that particular patient.

CASE REPORT

R. W., a sixty-three year old white man, entered the hospital on December 13, 1956 with a chief complaint of vomiting of coffee-ground–like material four to five times in the twelve hours prior to admission, and a feeling of faintness. The family history was non-contributory. The positive features of the patient's past history were an allergy to penicillin, a history of fractured ribs, and a history

of substernal and epigastric burning, some difficulty swallowing and relief with antacids of fifteen years' duration.

For several years the patient had had four to eight watery stools per day. Many of these had been clear, colorless and full of mucus. For approximately two weeks prior to admission, the patient had been feeling very weak. In the five days prior to admission, this weakness had become more severe and had been associated with anorexia, dizziness and an increase in the number and amount of rectal passages.

On the day of admission, the "diarrhea" had become very severe. Approximately twelve hours prior to admission, the patient began to vomit dark coffee-ground colored material. This occurred four to five times and was associated with weakness, dizziness and fainting.

The positive points in the physical examination on admission were: (1) temperature, 98°F.; (2) pulse rate, 126 per minute; (3) shallow respirations with a rate of 22 per minute; (4) blood pressure, 86/56 mm. Hg; (5) a defect with protrusion through the right inguinal canal and ring; (6) abdominal tenderness low in both the left and right lower quadrants; (7) rectal examination negative for abnormalities; (8) a clouded sensorium and (9) lethargy.

The laboratory findings on admission were as follows: hematocrit, 60 per cent; hemoglobin, 20.1 gm. per cent; white blood count, 15,000 per cu. mm. with 81 per cent polymorphonuclear leukocytes, 5 per cent lymphocytes and 8 per cent monocytes. An electrocardiographic study on admission disclosed sinus tachycardia with premature auricular and occasional nodal extrasystoles. Catheterization, ten hours after admission and 2,000 cc. of intravenously administered fluids later (1,000 cc. of 10 per cent invert sugar in distilled water and 1,000 cc. of Ringer's solution with 5 per cent dextrose), yielded 150 cc. of urine, which on examination was found to have a specific gravity of 1.015, to be acid in reaction, to be negative for sugar and protein, and to have 1 to 3 white blood cells and 75 to 100 hyaline casts on microscopic examination. A Levin tube was passed and 300 cc. of brownish-black, strongly benzidine-positive, solution was aspirated.

Emergency flat and erect films of the abdomen revealed gaseous distention of the large and small bowel, compatible with paralytic ileus. An emergency upper gastrointestinal series was performed twenty-four hours after admission in an attempt to reveal the source of the blood in the stomach, and disclosed a large hiatus hernia with narrowing and irregularity of the lower esophagus and an ulcer crater on the lower anterior aspect of the esophagus.

Blood chemistries were drawn fourteen hours after admission and gave the following results: blood urea, 116 mg. per cent; serum chloride, 78 mEq./L.; serum sodium, 119 mEq./L; serum potassium, 3.4 mEq./L.; serum albumin, 4.9 gm. per cent; globulin, 2.5 gm. per cent; serum van den Bergh, 1.0 mg. per cent indirect phase and 0.0 direct phase; thymol flocculation, negative; alkaline phosphatase, 5.0 Bodansky units; and cholesterol, 428 mg. per cent. Bleeding, coagulation, and prothrombin activity times and platelet counts were within normal limits.

Measurement of the patient's rectal output yielded the surprising figure of about 700 cc. per day. Analysis of this clear mucous material revealed the following values: chloride, 140 mEq./L.; sodium, 151 mEq./L.; and potassium, 15 mEq./L.

Blood volume studies were made after thirty-six hours of active treatment, using the Evans blue dye method. The patient's plasma volume was 2,175 cc. (normal, 2,950 cc.), the patient's blood volume was 4,089 cc. (normal, 4,900 cc.) and the red cell mass was 1,914 cc. (normal, 1,950 cc.). The patient had received a total volume of 6,300 cc. intravenously (plus 2,000 cc. orally) up to the time of the blood volume determinations with 300 cc. of this being whole blood, 3,000 cc. of 10 per cent invert sugar in distilled water, 2,000 cc. of Ringer's solution in 5 per cent dextrose solution and 100 cc. of 5 per cent sodium chloride solution. Vitamins were administered intravenously. The patient's urinary output increased from 250 cc. in the first twenty-four hours to 1,300 cc. in the next twelve hours. In the third twenty-four–hour period after admission, the patient received 3,800 cc. orally, 1,300 cc. intravenously (1,000 cc. of 10 per cent invert sugar solution, 300 cc. of 5 per cent sodium chloride solution). The urinary output during the same period was 3,075 cc.; the rectal loss was approximately 700 cc.

Over the next twenty-four–hour period (the fourth since admission) the patient received 3,340 cc. orally, 1,400 cc. intravenously (1,000 cc. of Ringer's solution in 5 per cent dextrose solution with 40 mEq. of potassium chloride added, and 400 cc. of 10 per cent invert sugar solution in 0.9 per cent sodium chloride solution). His output for this same period was 2,750 cc. of urine and 700 cc. of rectal discharge. On this day, sigmoidoscopy was carried out. A papillary, cauliflower-like, glistening, velvety-looking mass was seen on the anterior wall, at a point approximately 12 cm. from the anus and extending over a distance of 9 cm. In addition, there were internal hemorrhoids and an anal papilloma. Multiple biopsy specimens were taken and were read as a papillary or villous adenoma.

At this point, the patient was mentally alert and feeling much better. His lethargy on admission had disappeared. Blood pressure was 130/90 mm.

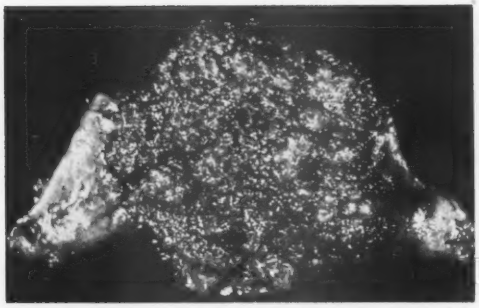

FIG. 1. Gross appearance of the villous adenoma following resection.

FIG. 2. Photomicrograph of the villous adenoma showing areas of glandular atypy and marked cellular dedifferentiation but no carcinomatous ulceration.

Hg. and pulse 86. The pertinent blood chemistry values were: urea, 93 mg. per cent; chlorides, 106 mEq./L.; CO_2, 22 mEq./L.; sodium, 129 mEq./L.; potassium 3 mEq./L.; cholesterol, 283 mg. per cent; calcium, 8.7 mg. per cent; and phosphorus, 2.1 mg. per cent.

At this point, the patient's blood volume studies were repeated, with the plasma volume being 2,475 cc., blood volume 4,207 cc., red cell mass, 1,732 cc., and the hematocrit 47 per cent. The patient was still deficient in plasma volume.

Over the next twenty-four–hour period (the fifth) the patient's intake was 2,940 cc. orally, 2,600 cc. intravenously (2,000 cc. of 10 per cent invert sugar solution in 0.9 per cent saline solution, 600 cc. of 5 per cent dextrose solution in 0.9 per cent saline solution). The output was 1,375 cc. of urine and 700 cc. of rectal secretions. Tests of the stool were negative for ova and parasites.

Over the sixth twenty-four–hour period after admission, the patient's rectal discharge increased to 2,500 cc. and the urinary output was 1,100 cc. The intake for this period was 1,950 cc. orally and 2,000 cc. intravenously (10 per cent invert sugar solution in 0.9 per cent saline solution). The blood chemistry tests revealed: urea, 34 mg. per cent; serum sodium, 149 mEq./L.; serum potassium, 2.9 mEq./L.; serum chlorides, 105 mEq./L.; and carbon dioxide 23 mEq./L. Tests of the urine were negative for acetone and on microscopic examination specimens showed 6 to 14 white blood cells and 2 to 8 casts on a high power field. The patient was clinically well, alert and in excellent spirits. His blood pressure was 130/70 mm. Hg. A barium enema was administered and an intussuscepting mass was noted in the mid-sigmoid with partial obstruction of the retrograde flow of barium.

The patient was prepared for operation with orally administered neomycin and cleansing enemas for forty-eight hours. On December 21, 1956 resection of part of the sigmoid and the rectosigmoid with end-to-end anastamosis and transverse colostomy were performed for an intussuscepting tumor beginning in the mid-sigmoid and presenting below the level of the peritoneal reflection. The tumor mass measured approximately 10 cm. by 8 cm. and was raised 4 cm. above the mucosal surface. This tumor occupied almost the entire lumen and was soft, sessile, broad based, polypoid, reddish gray, and velvety in appearance. (Fig. 1.) There was no palpable induration. Microscopic examination disclosed an extensive villous adenoma of the rectosigmoid, showing areas of glandular atypy and marked cellular dedifferentiation but no carcinomatous alteration or invasion of the wall. (Fig. 2.)

The patient's postoperative course was essentially uneventful. The wound healed per primam. Neomycin solution (100 cc. of 0.5 per cent solution) had been used to irrigate the peritoneal cavity and the layers of the abdominal wall. The subcutaneous space culture was negative at the time of the skin closure [6,7]. At the time of discharge, January 12, 1957, the blood chemistry values were all normal (urea 27 mg. per cent, sodium, 143 mEq./L., potassium 4.5 mEq./L.), the urinary findings were negative, the hematocrit was 42 per cent, and the colostomy was functioning well and regularly (irrigations twice daily). Antacids, antispasmodics and diet were prescribed for the esophageal ulcer, esophagitis and diaphragmatic hernia.

The patient was hospitalized a second time from April 15 to April 23, 1957. Repeat sigmoidoscopy and coloscopy were carried out. A small benign telangiectatic polyp of the transverse colon, approximately 5 cm. distal to the orifice of the distal limb, was excised, as was an inflamed anal papilloma. The results of a barium enema were negative for abnormalities. A gastrointestinal series revealed no evidence of esophagitis or esophageal

ulceration although the diaphragmatic hernia was still present as a "minute hiatus insufficiency." Blood and urine studies were the same as those made at the time of discharge following the first hospitalization.

A third hospitalization occurred from July 8 to July 20, 1957. The transverse colostomy was closed on July 7, 1957. The postoperative course was uneventful. The patient was discharged on no medication, having regular bowel movements and with a normal electrocardiograph.

Since the time of the last hospitalization, the patient has been seen on several occasions for excision of five separate basal cell carcinomas of the face. An elective hernia repair is now contemplated. Repeat sigmoidoscopies (the last on July 8, 1958) have been normal.

COMMENTS

This patient illustrates beautifully the hyponatremia syndrome. It is not unlikely that he soon would have been in irreversible shock, had therapy not been begun when it was. From Table 1, it can be seen that the subject of this report presented with all but two of the recorded symptoms of hyponatremia, short of death: weakness, apathy, lassitude, giddiness, headache, subcutaneous dehydration, anorexia, vomiting, abdominal cramps, weight loss, oliguria, paralytic ileus, azotemia, confusion hypotension and peripheral circulatory collapse.

The fact that the hyponatremia was secondary to the daily loss of over 700 cc. of fluid per rectum makes this even more unusual. The rectal fluid was found to contain a high concentration of sodium, potassium and chloride, each of which was higher than that in the blood stream—sodium 161 mEq./L., potassium 16 mEq./L., chlorides 140 mEq./L. This loss had been going on for several years prior to admission. Apparently, the patient's oral intake had been enough to maintain some sort of balance. However, the increased deficit, the increased renal insufficiency and, probably, the increased amount of secretion in the period prior to admission were too much for the body's electrolyte and fluid balances.

Like others, described in the literature, the present villous adenoma occurred in the sigmoid colon of a sixty-three year old man. It was seen on sigmoidoscopy because it was intussuscepting into the rectum from the sigmoid. A barium enema demonstrated this clearly and operation confirmed it. The gross (Fig. 1) and microscopic (Fig. 2) pictures were characteristic of a benign villous adenoma measuring 10 by 8 by 4 cm.

The present case is interesting from the standpoint of symptomatology. In addition to an advanced state of hyponatremia (including shock), there was associated esophagitis and bleeding esophageal ulcer. The latter states were undoubtedly made worse by the hyponatremia induced paralytic ileus.

The patient whose case is presented herein also had another tumor, as reported in approximately a third of the cases [3]. A second benign polyp of the transverse colon and five separate basal cell carcinomas of his face were associated tumors in the present case.

The handling of the fluid and electrolyte problem in this patient was a very interesting one [2]. It was necessary to replace previous deficits of serum sodium and potassium as well as fluid volume (as reflected in the plasma and blood volume deficiencies). It was also necessary to keep up with the continuing loss of volume and electrolytes (insensible fluid loss, rectal and urinary losses). The judicious use of hypertonic saline solution (5 per cent) was the key to the rapid correction of the hyponatremic state. The hypokaliemic state was corrected primarily by the sodium replacement which made some of the extracellular potassium available for intracellular replacement whence it has originally come in an effort to increase the total blood cations and thus preserve electroneutrality. The renal insufficiency (as reflected in the urinary changes, diminished urinary output and elevated blood urea), was reversed by the treatment of the hypovolemic and dehydrated state with adequate total volumes of solution. There had also been some blood loss secondary to the bleeding from the esophageal ulcer associated with a large diaphragmatic hernia. The esophageal ulceration with bleeding was probably secondary to the esophagitis, associated with the diaphragmatic hernia and made worse by the generalized intestinal ileus with secondary gastric dilation and esophageal irritation.

It is important to note that this patient's abnormal urinary picture on admission (1 to 3 white blood cells per high power field and 75 to 100 hyaline casts per high power field) was a result of the hyponatremia and dehydration, and cleared after adequate therapy. It was not a result of intrinsic renal disease. This is borne

out by the completely negative urinary findings at the time of discharge.

The surgical procedure chosen was primary resection with end-to-end anastomosis. Transverse colostomy was performed because the patient's preoperative condition had been precarious and it was thought that there might be impaired healing on the basis of unmeasured cellular deficiencies. The resection was performed as if this had been a malignant lesion because of the observation that even with multiple biopsies, the carcinomatous area of villous adenoma might be missed [3].

One of the important conclusions from this case is the importance of making chemistry studies even if the patient presents no acute evidence of hyponatremia. For the state may be a borderline one and actually appear asymptomatic for a long time (apparently, in this patient, for years). To operate upon such a patient could prove lethal.

SUMMARY

1. A case is presented of a sixty-three year old white man with hyponatremia, secondary to an intussuscepting villous adenoma and associated with an esophageal ulcer, esophagitis and a diaphragmatic hernia.

2. The characteristics and treatment of villous adenomas are reviewed.

3. The state of hyponatremia and its treatment are described.

4. The use of hypertonic saline solution (5 per cent) is credited with the rapid cure of the present case.

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Leiomyosarcoma of the Rectum

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LEIOMYOSARCOMA of the rectum is a rare and highly malignant lesion. Recent experience with two cases has brought to our attention the general unfamiliarity with this disease. For this reason the following cases are reported.

CASE REPORTS

CASE I. R. B., a fifty-six year old man, was well until two months prior to admission, when alternating constipation and diarrhea developed which lasted one week. His physician at this time found a rectal mass and advised further investigation. The patient delayed until increasing constipation and tenesmus forced him to seek treatment. There had been no blood in the stools. Physical examination revealed pallor of all mucous membranes and a smooth liver edge palpable 3 fingerbreadths below the costal margin. A firm, polypoid, ulcerated mass was felt on the posterior rectal wall, 5 to 6 cm. from the anal verge. Biopsy showed a leiomyosarcoma.

Laboratory tests were normal except for hemoglobin which was 10.8 gm. per cent, thymol turbidity 8.0 units, prothrombin level 55 per cent of normal. X-ray films of the chest and barium enema were negative for abnormalities.

The clinical course was as follows: After several days of preparation with intestinal antibiotics and transfusions, abdominoperineal resection was performed. No evidence of local extension or distant metastasis was noted. No explanation was found for the abnormal liver function tests. Recovery was uneventful until the fifth postoperative day when a pulmonary infarct developed. This was treated by bilateral superficial femoral vein ligation, followed by heparinization. The patient convalesced rapidly thereafter, and was discharged in good condition.

On pathologic examination the tumor was found to be a polypoid mass 10 cm. in diameter with a broad stalk arising from the posterior rectal wall, 6 cm. from the anal verge. The bowel wall underlying the tumor and all lymph nodes were free of tumor.

The patient appears entirely well with no evidence of disease nine months postoperatively.

CASE II. C. M., a thirty-five year old man, was admitted for treatment of a rectal tumor. He had been well until two and a half years prior to admission, when he began to experience intermittent sharp pain in the rectum not related to bowel movements. About one year before admission the pain became excruciating, particularly with defecation. He deliberately restricted his diet in order to diminish the frequency of bowel movements. He was told he had an "inflammation of the bowel" by his family physician, and was directed to use suppositories. Increasingly severe and persistent pain resulted in admission to the hospital. There had been no blood in the stools. There had been a weight loss of 20 pounds.

Physical findings were within normal limits except for the rectal examination. A firm, bulky, submucous tumor, 4 cm. in diameter, was found arising from the posterior rectal wall about 2 cm. above the dentate line. The mass was not fixed and there was no mucosal ulceration. Pressure on this mass caused pain. All laboratory studies were within normal limits. X-ray films of the chest and barium enema examination were normal.

The clinical course was as follows: After suitable preparation, an excisional biopsy was performed. The tumor seemed to shell out of its bed, although there was no definite capsule. Pathological examination revealed this to be a leiomyosarcoma. One week later an abdominoperineal resection was performed. The specimen at this time showed several microscopic foci of residual leiomyosarcoma. There was no evidence of metastasis in the lymph nodes. Convalescence was uneventful. The patient appears to be well with no evidence of disease nine months after his discharge from the hospital.

COMMENTS

Leiomyosarcoma of the rectum is uncommon. It is estimated to occur once in every 3,000 rectal tumors [1]. Unfamiliarity with its clinical

course and highly lethal potentiality often leads to improper management.

The signs and symptoms of this tumor are like those of any rectal neoplasm, although as a rule, these tumors are larger than carcinomas when first seen. This may be due to their origin in the submucous layers with only secondary involvement of the mucosa. The presence of a firm, rubbery, submucosal tumor in the rectum should suggest this diagnosis. Biopsy should be performed under direct vision and through mucosa if necessary. The distinction between leiomyoma and leiomyosarcoma is difficult by inspection unless fixation to surrounding tissue and ulceration of the overlying mucous membrane are present. Although these sarcomas appear to be encapsulated, in reality they infiltrate the musculature of the bowel wall. Spread is by vein and local extension [2].

Case analysis has shown the futility of attempting local excision of these tumors, the incidence of local recurrence being about 25 per cent [2,3]. This fact is emphasized by Case II, whose specimen obtained at the second operation revealed residual foci of tumor after presumably adequate local excision. Anderson et al. [1] stress the poor prognosis, reporting the death of nine of ten patients in from two to fifteen years, the average life span being 5.2 years. In his series of ten patients, only two were subjected to abdominoperineal resection.

It is our opinion that nothing short of radical abdominoperineal resection can be considered adequate surgery for this disease. Local excision invites disaster.

SUMMARY

1. Two cases of leiomyosarcoma of the rectum are presented.

2. Submucosal rectal nodules should suggest the possibility of leiomyosarcoma.

3. Experience has shown that attempts at local excision are followed by a high rate of local recurrence with associated poor prognosis.

4. We believe that radical abdominoperineal resection is the treatment of choice.

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Situs Inversus Totalis

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In reporting this case we wish to bring forth the importance of recognising the condition of situs inversus totalis in the prevention of errors in the diagnosis and treatment of surgical infections in patients with this condition.

CASE REPORT

A cadaver of a woman about forty years of age was received in this department for use in operative surgery at the postgraduate examinations. One of the candidates was asked to perform cholecystectomy. During this exercise the candidate could not feel the gallbladder as usual on the right side. Being puzzled he accidently put his hand on the left side and felt the edge of the liver on that side. This was how the condition of situs inversus was detected. The body was later completely dissected and the following anatomical findings were observed:

The condition of the thorax was as follows (Figs. 1 through 3): The heart was found in the right hemithorax (dextrocardia) with its apex pointing to the right side. The left ventricle formed the right border of the heart. The right ventricle lay in front of the left ventricle, showing that the rotation of the heart had taken place from side to side and not from front to back. The aortic arch and the descending thoracic and abdominal aortas lay on the right side of the midline of the body. The great arteries arising from the aortic arch showed complete reversal. The innominate artery gave off the common carotid and subclavian arteries on the left side, and the common carotid and the subclavian arteries arose separately from the aortic arch on the right side. The superior and inferior vena cava were on the left side. The vena azygos arched over the root of the left lung to join the superior vena cava. As the lungs were diseased and there were many adhesions, the relations of the lobes of the lungs could not be observed.

The condition of the abdominal viscera was as follows (Fig. 4): Here too the classic mirror image

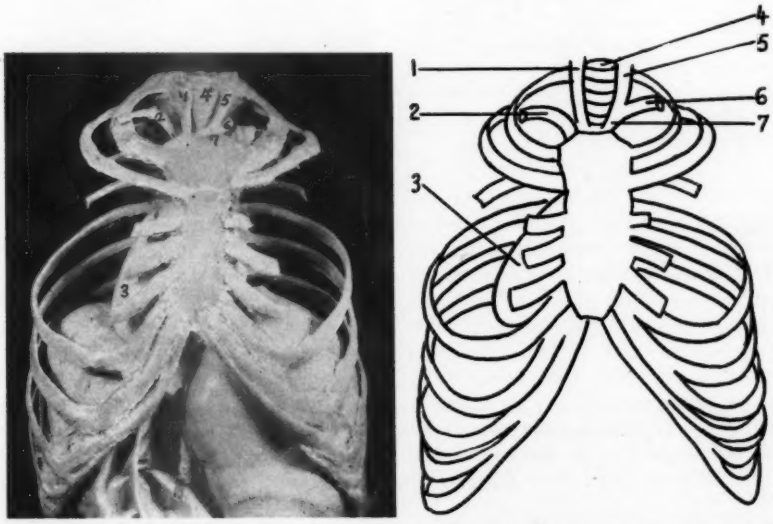

Fig. 1. (1) Right common carotid artery. (2) Right subclavian artery. (3) Heart. (4) Trachea. (5) Left common carotid artery. (6) Left subclavian artery. (7) Innominate artery.

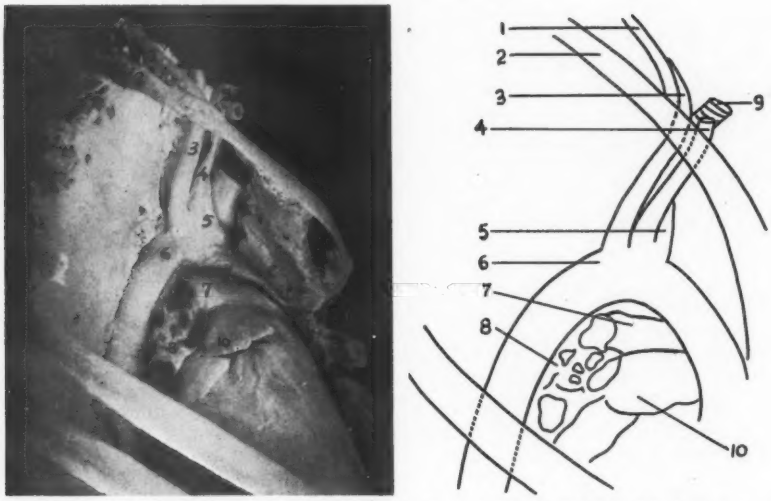

FIG. 2. Right side of thorax. (1) First rib. (2) Second rib. (3) Right subclavian artery. (4) Right common carotid artery. (5) Innominate artery. (6) Arch of aorta. (7) Right pulmonary artery. (8) Root of right lung. (9) Trachea. (10) Heart.

positions of the viscera were found. The stomach and spleen were in the right hypochondriac region. The liver and gallbladder were in the left hypochondriac region. The duodenal loop was on the left side with the head of the pancreas in its concavity. The body of the pancreas and its tail were situated across the posterior abdominal wall from left to right. The mesentery was found running obliquely from the right side of the midline to the left iliac fossa where the caecum and appendix lay. The ascending colon was on the left side. The descending colon was on the right side and the transverse colon crossed from the left to the right side. The sigmoid colon with its mesocolon was found on the right pelvic brim.

No other abnormalities were noted.

COMMENTS

The congenital condition of situs inversus with dextrocardia is more common than dextrocardia without situs inversus or situs inversus without dextrocardia. Blegen [1] in reviewing a series of 144 cases of situs inversus found complete (both thoracic and abdominal) situs inversus in 125 cases, and incomplete situs inversus in only nineteen cases. This suggests that all patients with dextrocardia should be investigated radiologically to determine the position of the appendix and other abdominal viscera.

The percentage of occurence of this condition is not known and is widely variable. Blegen puts it as 0.002 to 0.1 per cent. Prescott and Zollinger [7] reported about 475 cases as recorded in the literature, and stated that the incidence in a number of series combined (totaling about 600,000 cases) was a little more than 1 in 10,000. Mayo and Rice [6] found complete situs inversus in 76 of 1,551,047 patients registered at the Mayo Clinic, an incidence of 1 in 20,000. Chudnoff and Shapiro [4] found the incidence as 1 in 5,000 in their review.

We have recorded only one such case, presented herein, in 1,272 cadavers received and examined in our department from 1946 to 1958.

Situs inversus totalis is not an anatomical curiosity but is of great surgical importance. Failure to recognise this condition may lead to incorrect diagnosis, inability to carry out the operation initiated, and even an incision on the wrong side. This is indicated by Blegen who reported 144 cases of situs inversus in which the patients underwent surgical treatment. He states that in 55 per cent of the cases the condition was recognised before surgery, in 32 per cent during surgery, and in 13 per cent not until after surgery. Furthermore, he states that in 45 per cent of the cases, the diagnosis was incorrect. In 31 per cent an incorrect incision was made, and in 10 per cent the abdomen was closed without any surgical procedure being undertaken.

The two conditions in which situs inversus is

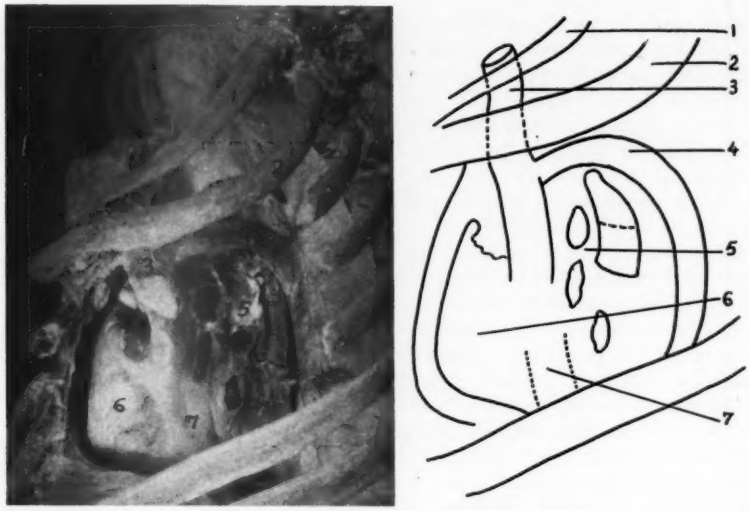

FIG. 3. Left side of thorax. (1) First rib. (2) Second rib. (3) Superior vena cava. (4) Arch of vena azygos. (5) Root of left lung. (6) Heart. (7) Inferior vena cava.

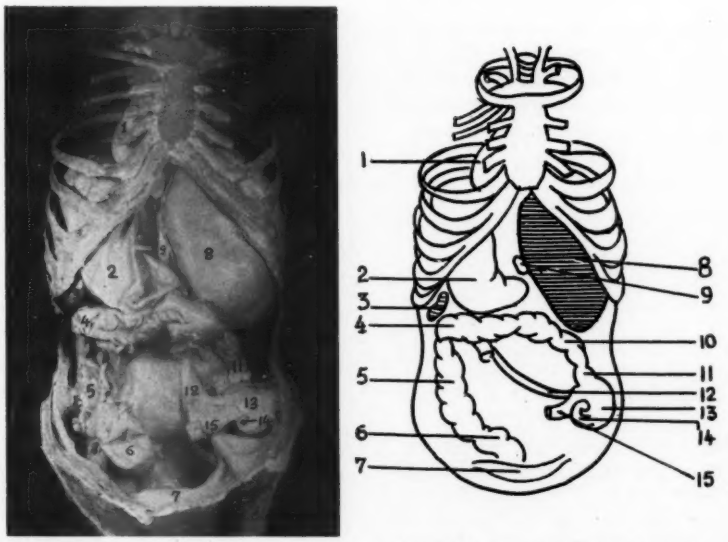

FIG. 4. (1) Heart. (2) Stomach. (3) Spleen. (4) Splenic flexure. (5) Descending colon. (6) Pelvic colon. (7) Uterus and fallopian tubes. (8) Liver. (9) Gallbladder. (10) Hepatic flexure. (11) Ascending colon. (12) Root of mesentery. (13) Caecum. (14) Vermiform appendix. (15) Terminal part of ileum.

of particular importance are diseases of the appendix and the gallbladder. Block and Michael [2] as well as Prescott and Zollinger [7] have reported appendicitis in a patient with situs inversus and have indicated two pitfalls in such cases. In one case the patient had pain in the right iliac region, and during surgery the appendix was found in the left iliac fossa. In such a case the operation would be performed on the wrong side. In the other case the pain was felt in the left iliac region. In such a case failure to recognise situs inversus would lead to an incorrect diagnosis. Cholst in quoting the literature stated that in only 50 per cent of forty-six patients with appendicitis and situs inversus was the chief symptom of pain on the same side as the appendix (i.e., left iliac fossa). Blegen reported on fifty-seven patients with appendicular disease and situs inversus and found that the pain was located in the right iliac region in twenty-one patients, in the left iliac region in thirty-two and throughout the lower part of the abdomen in the remaining four.

Biliary pain in contrast to the pain of appendicitis is usually found on the same side as the diseased organ (i.e., in the left upper quadrant of the abdomen in situs inversus). Wood and Blalock [10], in reviewing this condition and reporting a case of their own, found the pain from disturbances of the gallbladder in the upper left quadrant in eleven of the sixteen patients with gallbladder disease and situs inversus.

SUMMARY

1. A case of situs inversus totalis detected in a cadaver is reported.

2. By reviewing the literature, the importance of recognising situs inversus totalis in clinical surgery and surgical treatment (with special reference to appendicitis and gallbladder disease), is brought to light. The incidence of the condition is cited.

Acknowledgment: We wish to record our sincere gratitude to Dr. B. M. Desai, Professor of Anatomy, B. J. Medical College, Poona, India, for allowing us to publish this case and for his valuable suggestions and guidance in all stages of the preparation of this paper.

ADDENDUM

One of us (V. P. B.) has observed a similar case in which the patient was admitted under his care for the treatment of pneumonia. On screening the chest, dextrocardia was detected with a pneumonic patch on the left side. The patient was further investigated and barium meal examination of the gastrointestinal tract showed the classic mirror image positions of the abdominal viscera. On leaving the hospital the patient was given a certificate to that effect to avoid any surgical catastrophes in the future.

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Peritonitis, Caused by Surgical Glove Starch Powder, Treated with Steroids

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OCCASIONAL inflammatory reactions to surgical dusting powders employed to facilitate the drawing on of surgical gloves have been reported. With the use of starch powder it was hoped that this problem would be eliminated. However, recent reports [*21,22*] have shown that granulomatous inflammation can and does occur with starch, occasionally with serious consequences. We wish to report on a severe peritoneal inflammatory reaction due to starch particles, with progressive and rapid deterioration of the patient's condition. Because of the severity of the process, steroid therapy was initiated with an immediate regression of symptoms. The anti-inflammatory effect of the steroids appears to have been the decisive factor in the patient's recovery.

HISTORICAL REVIEW

It is important that a powder used with surgical gloves be unaltered by autoclaving, non-irritating to tissues, and absorbable from a surgical wound in a reasonably short period of time. Lycopodium and then talcum were the first powders used, but each proved irritating and non-absorbable. As early as 1916 Shattock [*1*] described a granuloma due to "silicious particles." However, most of our literature on the subject dates from Antopol's [*2*] article in 1933 describing granulomas from both lycopodium and talcum powder. From 1934 to 1944 many reports appeared stressing the danger of talcum powder in wounds. Several deaths implicating the reaction due to talcum powder are included [*3–14*].

Lee and Lehman [*15*] searched for a satisfactory substitute for talcum as a surgical glove powder, and in 1947 published the results of experiments with modified starch. Into the peritoneal cavities of each of ten dogs, they placed 1 gm. of starch powder (the equivalent of the washings from eight pairs of surgical gloves). It was found to be completely absorbed without demonstrable reaction three weeks after operation. In 1948, MacQuiddy and Tollman [*16*] observed that very little if any of this starch powder remained or caused deleterious effects after subcutaneous and peritoneal implantation in rabbits, guinea pigs and dogs. Alrich, Lee and Lehman [*17*] confirmed this in 1949, by further testing intraperitoneal reaction to the powder in dogs. In that same year, experiments on dogs and rats by Postlethwait, Howard and Schanker [*18,19*] indicated equally favorable response after the starch powder had been placed in peritoneal, pericardial, pleural and joint spaces.

However, since the acceptance of starch powder by the medical profession, further laboratory studies using 100 dogs led Lee et al. [*20*] to conclude that starch can produce a reaction in tissue. They showed that any powder contaminates a wound, producing a foreign body response as long as it is present. It was recommended that precautions be taken to avoid contamination of wounds, particularly with clumps or aggregate deposits that cannot be absorbed quickly.

There are now several reports in the recent literature of adverse reaction to starch powder in human beings. In 1955, Sneierson and Woo [*21*] reported two cases. One was a thirty-eight year old white man admitted with a malignant tumor of the left kidney, treated by nephroureterectomy. One month after operation, a mass in the left flank was noted associated with marked clinical signs suggesting sepsis. Following surgical exploration and excision, tissue studies revealed a granuloma due to foreign

bodies. These foreign bodies were identified as starch particles by using the iodine reaction test and polarized light. A second case requiring excision of a wound mass several months postoperatively was also reported. This too was identified as a foreign body reaction to starch powder.

In 1956, McAdams [22] reported many instances in which surgical specimens contained granules of absorbable starch powder on their surface coincident with their operative removal. In addition he described three patients re-operated upon after thirty-one, thirty-seven and seventy-nine days, respectively, in whom foreign body granulomas developed containing starch. One patient was a twenty-seven year old white woman in whom acute abdominal symptoms developed requiring intraperitoneal re-exploration four weeks after an elective cesarean section. Approximately 1,500 ml. of straw-colored fluid was obtained, and the entire peritoneal cavity was observed to be studded with 1 to 2 mm. nodules. Biopsy of a nodule disclosed a granulomatous reaction surrounding small particles of starch powder.

In a second case, a sixty-one year old white woman was re-explored because of abdominal and back pain, bloating, anorexia, nausea and fever occurring several weeks after cholecystectomy for cholecystitis and cholelithiasis. Multiple adhesions with many 1 to 2 mm. nodules on the peritoneal surface and bowel serosa were observed. Biopsy revealed these to be foreign body granulomas, consisting of inflammation around small, irregularly shaped starch powder granules.

CASE REPORT

In January 1958, a twenty-nine year old white woman was admitted to the Lenox Hill Hospital with chronic disease of the gallbladder. Cholecystectomy and common duct exploration, as well as a complete manual abdominal exploration were performed on January 28, 1958. The postoperative period was satisfactory, except for unexplained persistent fever, ranging from 100° to 101°F., until discharge on the tenth postoperative day.

One month after discharge the patient was readmitted, complaining of occasional pain in the left lower quadrant of the abdomen of two weeks' duration. This had become severe and constant and was accompanied by anorexia, nausea, and vomiting for three days prior to admission.

Physical examination revealed an acutely ill woman with a temperature of 102.4°F. The abdomen was tender to direct palpation throughout but particularly in the left lower quadrant. It was soft, not distended, without spasm, guarding or rebound tenderness. There were no palpable masses or organs. Pelvic and rectal examination revealed only moderate tenderness high on the left side.

The results of laboratory studies were as follows: hemoglobin 12.2 gm. per cent, white blood cell count 10,250 per cu. mm., with 74 per cent polymorphonuclear cells, 20 per cent lymphocytes, 3 per cent monocytes and 3 per cent eosinophils. The serum amylase was 57 units, alkaline phosphatase 3.1 Bodansky units, and serum bilirubin 0.5 mg. per cent. The results of urinalysis were reported as normal. The erythrocyte sedimentation rate was 80 mm. in one hour, while repeated leukocyte counts on the second, third, and fourth hospital days were essentially unchanged. Roentgen studies of the abdomen showed an increasing diffuse dilation of loops of both small and large bowel. An intravenous pyelogram and roentgenograms of the chest were normal.

The patient's condition became worse, manifested by increasing abdominal pain and persistent fever of 100° to 102.6°F. By the morning of the fourth hospital day, the abdomen was tense, distended and tympanitic. Diffuse direct and rebound tenderness was present. Laparotomy was performed on the fourth hospital day, six weeks after the initial surgery on the gallbladder. A provisional diagnosis of intra-abdominal abscess was made.

On exploration, the peritoneal cavity contained a large quantity of straw-colored fluid along with many adhesions. The omentum and appendices epiploicae of the descending and sigmoid colon were indurated and friable, having a pebbly appearance and texture. The pelvic peritoneum was studded with tiny nodules, each about 1 mm. in size. The small bowel was distended but for the most part the serosa appeared normal. No organic intestinal obstruction was present nor was there any evidence of an intraperitoneal abscess. Pieces of the omentum and an appendix epiploica of the sigmoid were taken for biopsy, and specimens were taken of the peritoneal fluid for bacteriological culture. A postoperative diagnosis of acute plastic peritonitis was made.

During the first four postoperative days, the patient continued to complain of severe abdominal pain and the abdomen remained distended in spite of nasogastric suction. Her temperature ranged constantly from 101° to 103.4°F. On the fourth day, the hemoglobin was 8.6 gm. per cent and white blood cell count 10,800 per cu. mm. The serum electrolytes and blood urea nitrogen were normal. By the morning of the fifth postoperative day her condition had severely deteriorated, and the patient was placed on the critical list. At this time, intramuscular administration of hydrocortisone (Solu-Cortef,® 300 mg. a day) was started, and the patient

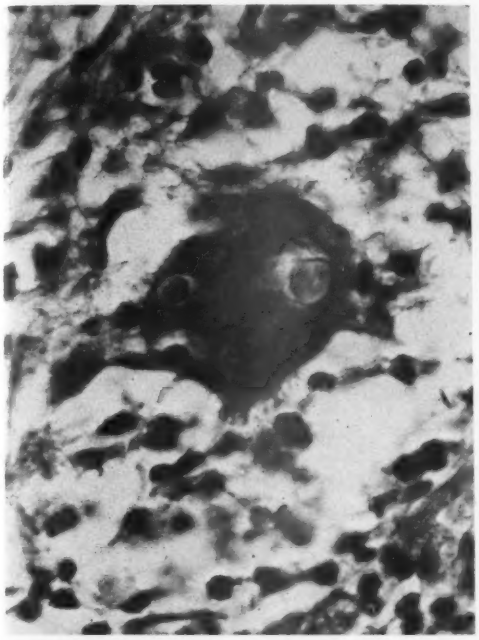


FIG. 1. A section through the granulation tissue that replaced much of the omental fat shows a characteristic foreign body giant cell containing a starch particle. Diagnostic blue staining of the particle occurred with Lugol's iodine solution.

was given a transfusion of 1,000 ml. of whole blood. Streptomycin and isoniazid (INH®) were also added to the medication regimen.

Within twelve hours, the patient became afebrile for the first time since admission, had much less abdominal tenderness and was passing flatus. In thirty-six hours the abdomen was soft and flat with only minimal tenderness remaining. The Levin tube was removed and oral feedings, found to be well tolerated, were given. On the eighth postoperative day, the oral administration of prednisone was started and parenterally administered steroids were discontinued.

The patient progressed well throughout the remainder of her hospital stay. On the eighth postoperative day, her weight was noted to be 87 pounds (normal weight, 90 pounds). By the fifteenth postoperative day her weight had fallen to 78 pounds. A high caloric, high protein diet with interval feedings, orally administered potassium, and testosterone proprionate were given with subsequent weight gain. The response to a skin test for starch sensitivity was negative. At the time of discharge on the twenty-second postoperative day, the patient was eating well, gaining strength and weighed 84 pounds. Streptomycin and isoniazid were discontinued at the time of discharge. In follow-up clinic, two weeks later, the patient's weight was 90 pounds. The administration of prednisone and testosterone was then discontinued, thirty-six days after operation and thirty-one days after initiation of steroid therapy. Further convalesence was uneventful. However, six months later, during a clinic visit, the patient did complain of persisting, occasional bouts of mild abdominal cramps. Physical examination was entirely normal.

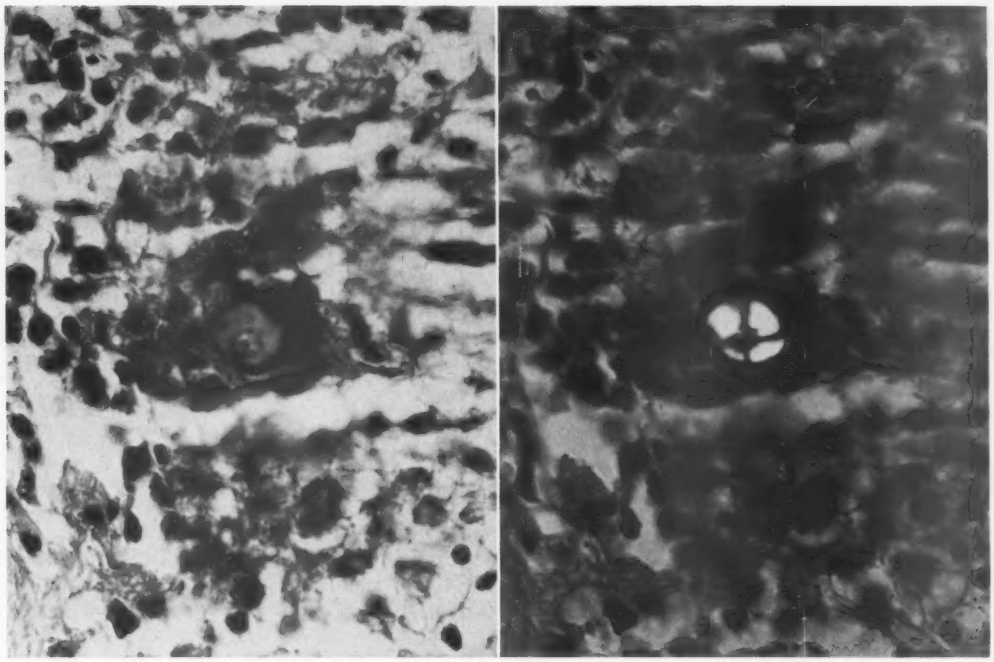
Laboratory examination of the biopsy specimen revealed that the omental fat was partially replaced by inflammatory, granulation tissue. (Figs. 1 and 2.) It consisted chiefly of epithelioid cells and vascular elements forming characteristic tubercle-like structures. There were may multinucleated foreign body giant cells. Within some of these giant cells, irregularly shaped fragments of double-refracting material were noted. A pathologic diagnosis of plastic peritonitis, secondary to foreign bodies identical with starch particles was made.

COMMENTS

This case is an example of the severe response that can result from unabsorbed foreign particles in tissue. The unexplained low fever following the cholecystectomy and abdominal exploration, and later the onset of abdominal pain about four weeks after operation, indicate that the reaction was gradual and progressive. Almost six weeks was required for it to reach the severely acute phase. A marked similarity is noted when this case is compared with the cases reported by others, particularly those of McAdams [22]. The high fever, the acute abdominal signs, and the free fluid in a nodule-studded peritoneal cavity are conspicuous by their repeated occurrence.

The possibility was considered that this reaction might be an allergic phenomenon. The patient did claim a prior reaction to penicillin; however, all other allergic diseases and reactions were denied. It was noted particularly that on microscopic examination of the tissue an eosinophilic cellular response, as seen in allergic processes, was absent. This, along with the skin test which was negative for starch sensitivity suggests that probably no association exists between an allergic response and this foreign body inflammation.

A bacterial etiology also appears unlikely in view of negative cultures of the peritoneal fluid for both aerobic and anaerobic organisms. Microscopically, however, the pathology specimen was not unlike that seen with a Koch's bacillus infection. Therefore, in view of the



2A 2B

FIG. 2. A, another section through granulation tissue showing the typical starch particle in a giant cell. B, the same section of granulation tissue as seen in (A), viewed with polarized light. The Maltese cross formation of the starch granule is demonstrated.

possible tuberculous etiology, although remote, streptomycin and isoniazid (INH) were given concomitantly for protection when steroid therapy was initiated on the fifth postoperative day. When further examination microscopically, along with negative tuberculin skin tests and bacteriologic reports, reassured us of the absence of tuberculosis, these drugs were then discontinued.

The steroid agents are well known for their anti-inflammatory effect. Thus, as the patient's condition progressively deteriorated, it was decided to use steroid therapy to suppress the irritating effects of the starch particles. The patient responded promptly, showing a marked improvement in her general condition as well as a fall in temperature to normal range. The catabolic effect of the prednisone, along with the other factors conducive to weight loss, was successfully countered with a high caloric diet, orally administered potassium, and the anabolic agent, testosterone proprionate.

It is thus apparent that modified starch as a surgical glove powder cannot be considered benign. Any powder will act as a foreign body, stimulating a response as long as it remains in the tissue, and starch is no exception. The intensity of the inflammatory reaction produced is variable, depending mostly on the size of the particles implanted and the time required for absorption. Clumps, which are particularly slow in being absorbed, constitute the major hazard. This has been concluded on a clinical basis as well as in the laboratory [*20–22*].

At surgery, powder enters and contaminates a wound in many ways. As the surgeon's hand with an unwashed glove explores or retracts, or each time a glove perforation occurs, powder is implanted. The air-borne mist, that is loosed as starch is sprinkled upon the hands of the surgeon prior to donning his gloves, may send the tiny particles over the operative field. Sponges, instruments and suture material can all be carriers of powder to the wound.

It is apparent that glove powder, regardless of type, must be kept out of a surgical wound.

This is easily accomplished by washing the gloves immediately prior to starting surgery. The use of either wet gauze or the wash basin itself will prove most efficacious in eliminating this potential hazard. The wash basin, cloudy with powder from washed gloves, gives evidence of the quantity of powder that could easily have been implanted.

After all factors are considered, it nevertheless must be recognized that the starch powder used in operating rooms today is a relatively satisfactory agent. The incidence of adverse reaction is minimal considering the number of operations performed. Compared to the era of lycopodium and talcum, it is understandable why surgeons today tend to look upon starch as benign. However, previous reports [*21,22*] as well as the case described herein should be a reminder that even this useful agent has its limitations.

SUMMARY

A case of acute postoperative peritonitis, caused by a foreign body granulomatous reaction to surgical glove starch powder, is presented. The patient was successfully treated with steroids, initiated when she approached a critical status. Following a historical review of reactions to surgical glove powder, particularly recent articles implicating starch, a warning is given that modified starch powder as used in modern operating suites is potentially dangerous unless precautions are observed to prevent the powder from entering the wound.

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The Nasogastric Tube As a Cause of Esophagitis and Stricture

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A CASE of esophageal stricture is presented in which a Levin tube appeared to be a causative or precipitating factor. Symptoms developed six months after a brief period of gastric decompression that was incidental to abdominal surgery. Dysphagia and retrosternal pain were the complaints.

This patient presented a problem in differential diagnosis between carcinoma and benign stricture; therefore, the stenosed esophagus was exposed by thoracotomy. A diagnosis of benign stricture was established and the stricture was relieved conservatively by mobilization and myotomy. Follow-up six months after operation (at the time of this writing), revealed no recurrence; the swallowing mechanism was normal.

Despite a lack of direct evidence that indwelling tubes of the Levin or other type may be wholly or partly responsible for ulceration and subsequent stricture of the esophagus, there is general warning in the literature that intubation predisposes to stricture [*1–4*]. This warning is worth heeding because there are indications that such a tube can precipitate esophagitis which in turn leads to fibrosis and stricture. It is probable that predisposing factors are present when a gastric tube incites esophagitis and fibrosis. Only rarely is there evidence that the tube alone is responsible. Predisposing factors are strenuous vomiting, debility, previous esophagitis and obstructing gastrointestinal lesions.

Although stricture as a complication of esophageal intubation does not occur often considering its incidence when compared to the frequency with which tubes are used for intestinal decompression, still it is not a rare condition. It does occur, and when it does, it is serious. Therefore, the factors that predispose to it should be regarded as danger signals. In the case reported herein, predisposing factors were not evident.

CASE REPORT

Mrs. G. W., seventy-two years of age, was hospitalized on September 3, 1957, for dysphagia and retrosternal pain of ten months duration. Although the patient had first experienced trouble in swallowing in November 1956, she traced her difficulty back to September when a Levin tube had "irritated" her throat.

In September, 1956, she had had an attack of acute appendicitis. The diagnosis was confirmed at laparotomy as gangrenous appendicitis, and the appendix was removed. The patient had been healthy and active until six days before the operation. Recovery from the appendectomy was uneventful until the third postoperative day when abdominal distention became very troublesome. She did not vomit. A gastric tube of polyvinyl plastic was passed nasally.

Because the patient complained almost continually about the tube "bothering her throat and chest," it was removed after twenty-four hours and was replaced by a rubber Levin tube. This tube also "bothered" her throat. Distention having been relieved, the rubber tube was removed twenty-four hours later. It was not needed again.

Three months later, in December 1956, difficulty in swallowing developed. The patient admitted to irregular "heartburn" for a month before dysphagia set in. This was noticed only with solid foods, particularly meat. At first she had trouble only irregularly, but after several months the symptoms appeared with every attempt to swallow solid foods. She experienced a delay in swallowing at the level of the lower half of the sternum. During the three months prior to September 3, 1957, she had restricted herself to liquids and very soft foods. Occasionally "large amounts" of food were regurgitated thirty or forty minutes after eating. At the time of admission there was delay and discomfort even with liquids.

The past history was non-contributory with the exception of the appendicitis. The patient was

FIG. 1. Preoperative x-ray film after barium swallow showing constricted area at level of tenth thoracic vertebra. Oblique view.

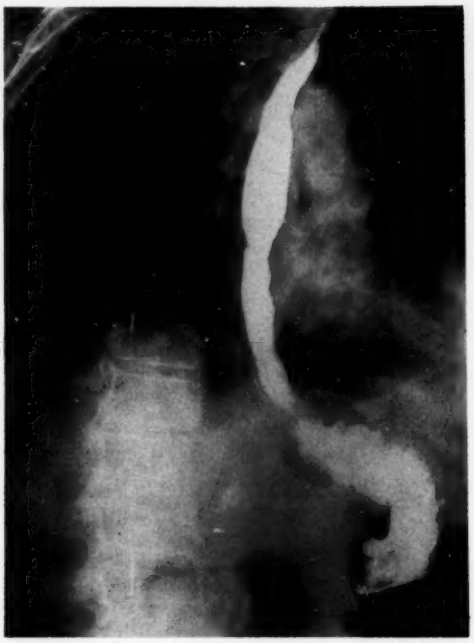

FIG. 2. Postoperative x-ray film showing normal width throughout the length of the esophagus. Oblique view.

alert and went about her usual tasks without difficulty. She was moderately obese, weighed 150 pounds and was 5 feet, 3 inches in height. Aside from moderate hypertension (180/100 mm. Hg) the physical examination revealed nothing unusual. The skin and subcutaneous tissues were of good texture. The weight loss of 10 pounds was not evident.

Upon x-ray examination barium swallow showed a normal upper swallowing mechanism, but an area of persistent narrowing 4 cm. in length was demonstrated in the distal third of the esophagus. (Fig. 1.) The constricted area tapered distally. There was no evidence of hiatus hernia.

The narrowed area was visualized by esophagoscopic examination and the instrument was passed through with only slight difficulty. The esophageal membrane above and below was normal in appearance. In the narrow zone the membrane was red and edematous. There was an oval eroded area with estimated measurements of 5 by 10 mm. The edge was elevated and irregular but it was not undermined. The area was stiff. Biopsy specimens showed chronic inflammation and fibrosis. A second esophagoscopic examination five days later produced the same results.

Despite the biopsies which showed only chronic inflammation, carcinoma was still entertained as a possible diagnosis. Dysphagia was the major symptom; heartburn, regurgitation and pain were minor. Careful review of the history failed to disclose a significant traumatic factor. For these reasons exploratory thoracotomy was elected in preference to bouginage.

Preoperative laboratory determinations were as follows: erythrocytes, 4,120,000 per cul mm.; leukocytes, 8,400 per cu. mm. with normal differential; hemoglobin, 12.7 gm. per cent; hematocrit, 41 per cent; and urea nitrogen, 15.2 mg. per cent. Urinalysis showed occasional granular casts and albumin, ten mg. per cent.

At operation the constricted area was readily identified. It measured 2 inches in length and its distal end was 3 inches above the diaphragm. The periesophageal tissues were stiff and adherent to the esophagus. The esophagus was mobilized and the muscular wall was divided vertically to the submucosa; the wall was thick and stiff. Careful palpation through the submucosa disclosed no lesion within the lumen, and the membrane was, therefore, left intact. The muscle layer was left open as in the Heller procedure. Recovery was uneventful.

Upon x-ray examination on the tenth postoperative day barium swallow showed a normal swallow-

ing mechanism. There was no evidence of delay or deformity.

Clinically the patient has had no further complaints. Follow-up x-ray examination after five months (Fig. 2) showed no abnormality of the esophagus.

COMMENTS

The role of gastric tubes in the etiology of esophagitis and stricture cannot be determined directly but it is probable that certain predisposing factors must be operative before an indwelling tube can produce significant damage to the esophageal membrane. Otherwise the complication would occur much more frequently than it does.

This does not imply that postoperative esophagitis is a rare condition. On the contrary, it is relatively common but it passes by unnoticed and reaches a healed stage before fibrosis and stricture take place. The symptoms are overlooked. Vinson and Butt [5] found esophagitis in 7 per cent of 3,000 subjects at necropsy, but the clinical records of these patients recorded symptoms of esophagitis in only 10 per cent of those who had the disease. Seventy-five per cent of the 213 patients with proved esophagitis had been operated upon only a short time before.

In respect to predisposing factors Douglas [3] has compiled a list of conditions that render the esophagus vulnerable to the trauma of a gastric tube. In 1956, he reported on five cases of esophageal stricture that developed without obvious cause and he compared these with twenty-three similar cases he was able to gather from the literature. Among these patients several factors were common to all.

In the majority of these cases Douglas found that abdominal operations had been performed a short time before, vomiting had been a prominent symptom and a gastric tube had been used for decompression. Dysphagia had developed after the tube had been removed. Radiologic and endoscopic investigations revealed a stricture in the lower third of the esophagus. Douglas emphasized the association of vomiting and esophageal intubation, and he pointed out that it is difficult to separate and assess the relative roles of vomiting and intubation. The retching of vomiting can tear the esophageal membrane.

Palmer [1] also recognizes the problem of separating vomiting and intubation as causative factors. He suggests that vomiting may act by "mechanically scouring the mucosa" to provide a contact with acid pepsin. To the Levin tube he ascribes the mechanism of actual surface trauma.

In the pathogenesis of benign and intrinsic strictures of the esophagus, membranous erosion precedes mural fibrosis. This is important; something must break the membrane, and herein lie the traumatic roles of vomiting and intubation. An inflammatory process develops beneath the broken and eroded membrane and this leads to fibrosis of the muscular wall. Regurgitated gastric secretions bathing the eroded surface act as an irritant, enlarge the raw area and prevent resolution.

Although acid peptic digestion by regurgitated gastric secretion is responsible for the persistence of erosions, it is unlikely that erosions are initiated by this mechanism. Regurgitation is a natural phenomenon to which the esophageal membrane is well adapted. The lower esophagus is bathed intermittently in the natural regurgitation of gastric juice, but the membrane is unaffected because it is coated and protected by secretions from the esophageal mucous glands [1,6,7]. Unless abnormal traumatic or physical factors come into play the mucous coat will protect the membrane.

Esophageal mucus is altered and diminished by the avitaminosis and dehydration that accompany debility and senility. In the exhausted and debilitated patient the esophageal membrane, dry and exposed, is highly vulnerable. If a traumatic factor is added to break the membrane, the natural gastric secretions, bathing the membrane at intervals, can induce erosion.

The necessity for using the Levin tube in the debilitated patient who is vomiting is obvious, yet it is such susceptible patients who can be harmed most by the tube. To the trauma of the tube is added the mechanical distortion of the cardioesophageal angle, a condition that prolongs the bathing of the lower esophagus in gastric secretion.

The importance of debilitation as a predisposing factor is illustrated in Bartels' survey of 6,000 necropsies in which he found eighty-two ulcerative esophageal lesions [8]. Of these, fifty-five or 67 per cent were postoperative, and all of the operations were difficult and extensive, or the patients were poor risks. Thirteen of the patients presented sepsis and six had ulcerative colitis with severe debilitation.

The length of time an esophageal tube remains in place does not appear to bear a direct relationship to the onset of esophagitis or to the occurrence of stricture. In some of the reported cases, as in that presented herein, the sojourn of the tube has been less than forty-eight hours. However, tubes have been kept in the eosphagus for months without complications [9]. Pareira et al. reported on the tube feeding of 240 malnourished patients for weeks and months; they had no trouble with esophageal ulceration. It is noteworthy that vomiting was infrequent among these patients. Vomiting makes the esophagus vulnerable. Palmer [1] postulates a "safe period" of about four days in the presence of predisposing conditions.

The location of these strictures in the lower third of the esophagus emphasizes the role of acid peptic digestion in maintaining an erosive esophagitis once it is set up by trauma. Certainly vomiting and intubation traumatize the middle and upper portions of the esophagus. However, strictures of this type are uncommon at these levels, probably because healing in the absence of irritation from acid pepsin takes place before fibrosis is initiated. Strictures at the level of the cricoid cartilage or perichondritis and stenosis of the larynx [4,10] are related directly to tube pressure because of the narrower channel and the more limited mobility of both the tube and the anatomical structures in these areas.

It becomes apparent that it is difficult to assess the relative roles of intubation, vomiting and predisposing factors in determining the etiology of postoperative esophagitis, ulceration and stricture. It is probable that the gastric tube leads to serious complications only in the presence of factors that predispose to esophagitis. Attention should be paid in the postoperative period to symptoms that suggest esophagitis: heartburn, sour stomach, substernal and epigastric burning sensations with pain referred to the head, neck and arms. When these symptoms are present, the tube should be used with caution.

SUMMARY

A case report of esophageal stricture is presented. A Levin tube used for intestinal decompression appeared to be a causative or precipitating factor. The role of the Levin tube in this condition is discussed in relation to other factors such as vomiting, debility and previous esophagitis. Caution is advised in the use of the Levin tube in the presence of factors that predispose to esophagitis.

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SPECIAL DEPARTMENTS

Surgery Court Cases

HOWARD NEWCOMB MORSE,* *Chicago, Illinois*

CLARK VS. STOWELL

Supreme Court of Oklahoma

315 P. 2d 269

This was an action by a patient against a surgeon to recover for personal injuries sustained because of alleged improper treatment administered after an automobile accident in which the patient was injured. The District Court of Tulsa County, Oklahoma, entered judgment for the surgeon, and the patient appealed.

The patient was involved in an automobile collision while riding as a passenger in an automobile driven by a third party. The accident occurred when the automobile driven by such third party collided with a train operated by the Oklahoma, Kansas and Gulf Railway Company. He was taken to a hospital in Tulsa and was there treated by the surgeon.

The patient alleged that the surgeon, in treating him, gave him a myelographic spinal test, which consists of injecting into the spinal column a colored fluid of some character so that an x-ray film will reflect a complete and accurate picture of the spinal column. He further alleged that this injection was given him without his knowledge and consent; that in giving such treatment his spinal column was punctured; that the injection given him was improper and negligently given in violation of the duty which a doctor owes to his patient; that as a result of such treatment he became violently ill. He suffered severe pain in his back, neck, head and arms and continued to have such pain. Subsequently, he was treated by various doctors for such condition, without beneficial results, and by reason thereof was unable to do any kind of work except for a short while at a time, and such condition persisted.

The surgeon defended on the ground that the patient's condition was due solely to the injury sustained in the automobile accident and not to any treatment administered to him. The surgeon admitted that he gave the patient the myelographic test but denied that such treatment was improper, and alleged that it was such test as is usually given by doctors under similar circumstances.

The Supreme Court of Oklahoma affirmed the decision of the court below. The Supreme Court declared: "Plaintiff offered no evidence tending to show that the fluid injected into plaintiff's spine was improper treatment, or that the doctor was in any manner guilty of negligence in administering said treatment, nor is there any evidence tending to show that the injection of the fluid into his spinal column is the cause of plaintiff's present condition and disability and, therefore, wholly insufficient upon which to submit the case to the jury."

WITCZAK VS. JOHNSON

District Court of Appeal of California

303 P. 2d 1091

This was an action by a patient against a surgeon for malpractice. The Superior Court of San Bernardino County, California, entered an order and judgment dismissing the patient's case, and she appealed.

The patient alleged that she employed the

* Counsellor at Law of the Supreme Court of the United States of America.

surgeon to diagnose and treat an ailment of her right leg, which was weak and diseased. The nature and extent of such ailment was unknown to the patient but was well known to the surgeon. The surgeon diagnosed it as a paralyzed nerve and more than a year later diagnosed it as peripheral neuritis. He treated the patient's condition by various injections not known to the patient but well known to himself. The patient further alleged that the diagnoses and treatment were improper and erroneous; that the injections were wrong and were harmful and injurious to her health; that as a direct and proximate result she sustained severe personal injury to her body and particularly to the right arm and right leg; and that the injury to the right leg consisted of a disease, strain, inflammation and deterioration of the muscles, ligaments, tendons, nerves, blood vessels and soft tissues thereof.

The District Court of Appeal of California reversed the order and judgment of the lower court. The District Court of Appeal held that the patient's complaint for the surgeon's malpractice stated a cause of action for malpractice, even though it could "have set forth, in more definite and certain terms, the issues to be met so that it might acquaint the . . . (surgeon) with the nature, source and extent of the cause of action."

The Diagnostic Corner

AN interesting type of injury of the upper extremity, the nature of which is often unrecognized, and the treatment of which, therefore, often results in numerous serious complications.

SIDNEY W. NELSON, M.D., *Columbus, Ohio*

From the Department of Radiology, The Ohio State University, Columbus, Ohio.

THE radiographs (opposite) are those of a seventeen year old housewife who fell on her outstretched left hand and forearm on the afternoon of the day of admission. These frontal and lateral films were made because of a painful swollen proximal left forearm and show clearly the nature of the lesion, which, if not treated properly, will almost certainly become complicated by one, or more, of a formidable group of difficulties. *What is your diagnosis?*

Please turn page for answer

Diagnosis

Fracture of the shaft of the ulna with associated dislocation of the head of the radius (Monteggia fracture-dislocation).

In the roentgenograms opposite note that the head of the radius does not articulate with the capitellum of the humerus (dotted lines) as it normally would, but is completely dislocated (arrows) to a position forward and slightly lateral to the lateral epicondylar region of the humerus. There is overriding of the fracture fragments of the ulna, and the fractured ulna is angulated forward. This type of fracture-dislocation comprises about 90 per cent of cases of Monteggia fracture-dislocation, about 10 per cent of the cases being of the flexion type. In the latter type of lesion the head of the radius is dislocated backward and the ulnar fracture is angulated backward.

Unfortunately in this type of injury the dislocation of the radial head is often not recognized. The fracture-dislocation is then treated as a simple fracture with much resultant pain and limitation of motion due to the unreduced dislocation of the radial head. Furthermore, unless the fractured ulna is satisfactorily immobilized by internal fixation in those cases in which the fracture is angulated anteriorly, there is a very high incidence of malunion, nonunion, and cross union between the radius and ulna at the level of the fracture. Although the complications are diminished in number when the condition is recognized and reduced by internal fixation, there is, nevertheless, an unfortunately high incidence of residual disability unless the treatment is instituted by a surgeon with experience in treating this type of lesion.

Inasmuch as the correct diagnosis and prompt treatment are of paramount importance, the x-ray films must be carefully interpreted at the outset. It is important to remember that the radius and ulna are intimately related to one another anatomically, and that it is extremely unusual to see a fracture of the shaft of the proximal ulna without either an associated fracture or dislocation of the radius. Thus, if a fracture of the proximal shaft of the ulna is not accompanied by a fracture of the radius at a similar level, the presence of a dislocation must be strongly suspected. Furthermore, if there is actual overriding or angulation of the fracture of the ulna without a similar injury to the radius, there is almost certainly an associated dislocation of the radial head, which is by far the most important aspect of the injury.

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Case Analysis Clinic

Pneumothorax—a surgical problem.

CHARLES V. MECKSTROTH, M.D., *Columbus, Ohio*

From the Division of Thoracic Surgery, Department of Surgery, The Ohio State University Health Center, Columbus, Ohio.

PATIENT V. B., a thirty-five year old white physician's wife, entered University Hospital with the history of having fallen off a horse several hours earlier. She complained of moderate pain on respiration over the left seventh, eighth and ninth ribs associated with increasing shortness of breath. The patient remained conscious during the entire time but complained of dizziness upon entering the emergency room. She had no previous pulmonary complaints.

PHYSICAL FINDINGS AND TREATMENT

There was pain on palpation over the left lateral chest area, especially over the seventh, eighth and ninth ribs. No definite crepitation or subcutaneous emphysema was felt. Breath sounds were markedly decreased over the entire left side of the chest.

The remainder of the physical examination was within normal limits. Although a cursory neurologic examination was negative, neurologic consultation was requested to rule out injury to the head.

The diagnosis of traumatic pneumothorax was made on the basis of history and physical examination. An upright chest roentgenogram showed 30 per cent collapse of the left lung, with fracture of the left eighth rib in the posteroaxillary line. The patient was prepared for closed thoracotomy. No premedication was given since the possibility of cerebral trauma was present. Using 1 per cent procaine for anesthesia, a preliminary needle aspiration confirmed the presence of pleural air. A No. 28 French-Robinson catheter was introduced through a trocar into the left pleural cavity at the level of the fifth intercostal space in the mid-axillary line. A free exchange of air showed the catheter to be in the correct position. It was then connected to underwater seal drainage and in turn to 30 cm. of water-constant negative pressure. There was an immediate egress of approximately 1,000 cc. of air from the pleural space. The patient complained of cough and pain, typical of a re-expanding lung.

A portable chest roentgenogram taken the following morning showed the lung to be expanded. The thoracotomy tube was changed to simple underwater seal drainage for twenty-four hours and was then removed. During her hospital stay the patient showed no significant neurological abnormalities. On the third hospital day she was discharged following fluoroscopy. Roentgenograms taken two weeks later showed continued full expansion of the left lung.

ETIOLOGY

Most patients treated for pneumothorax have no history of definite trauma. "Spontaneous" pneumothorax is usually due to ruptured emphysematous blebs. In this type of case "tension" pneumothorax is most frequently seen since the thin, relatively avascular tissue acts as a "check valve," letting air pass from the bronchioles to the pleural space but preventing its return by closing over the fistula. If untreated, this will produce mediastinal shift and collapse of the opposite lung.

Traumatic pneumothorax from a puncturing rib end, as in the patient described, generally produces enough local alveolar hemorrhage to nullify the "check valve" effect. This pulmonary hematoma resolves slowly over weeks or months. When a gunshot wound produces a pleurocutaneous fistula the problem of tension pneumothorax is non-existent, but an equally serious situation is present, that of a collapsed lung and mediastinal shift. This happens when the diameter of the fistula is about one-half that of the trachea. Temporary closure of the chest wound with available clothing may preserve life.

DIAGNOSIS

The clinical picture of angina pectoris can simulate a collapsed lung, especially on the left. Shock with chest pain, pallor, weak pulse and

shortness of breath can be misleading. Even though breath sounds are diminished in a suspected pneumothorax, a roentgenogram is necessary. If previous pleural pathology has produced adhesions, examination of a lateral x-ray film of the chest may prevent the surgeon from inadvertently placing a drainage catheter in a huge emphysematous bleb fastened to the chest wall. Care must be taken not to confuse a large emphysematous cyst with a pneumothorax. Tension pneumothorax is characterized by displacement of the trachea to the opposite side and a similar change in position of the point of maximum impulse.

The patient with a pneumothorax, regardless of etiology, becomes symptomatic because of alterations in intrathoracic pressure. Older patients with pulmonary emphysema, pulmonary fibrosis and decreased expansion of the chest cannot maintain the negative pressure required to expand the lungs. An extreme example of this is a large bronchopleural fistula in which the mediastinum flutters back and forth, producing paradoxical respirations. Even a so-called "10 per cent collapse" of a lung can produce shortness of breath because this anatomic 10 per cent represents 30 to 40 per cent of the functioning alveoli of that lung. The more centrally placed bronchi with their cartilaginous rings collapse very little under these conditions. In addition, the pain of respiration, reduced tidal volume and loss of differential circulation in the lung increase the effort necessary to maintain respiration.

TREATMENT

This depends upon the facilities available and the condition of the patient. Ideally a closed thoracotomy should be performed when the lung is more than 20 per cent collapsed as shown by roentgenography or when there is a smaller collapse if the patient is in respiratory difficulties. In male patients the tube is inserted in the second or third intercostal space in the mid-clavicular line. In females the mid-axillary line is used when possible at the level of the fifth intercostal space. Although simple underwater seal drainage will suffice in many cases, it is usually preferable to apply constant suction to the thoracotomy tube by way of a standard interposed suction controlling bottle. While it is obvious that some lungs expand by conservative treatment if given enough time, the patient's recovery can be hastened by the proper insertion of a drainage tube. I recently treated a patient by this method for recurrence of spontaneous pneumothorax. The lung expanded overnight. On the previous occasion one year of medical management was required for complete expansion, causing the patient to lose his job. In hemothorax this drainage often saves lives. In many patients decortication has been made unnecessary by the simple insertion of a thoracotomy tube. In some cases of traumatic pneumothorax, operative intervention is necessary to remove clotted blood and to suture leaking lung tissue.

If ideal facilities are not available and the patient is only slightly or moderately short of breath, transportation with medical surveillance is permissible. It is better to have a lung partially collapsed in a relatively sterile pleural space than to initiate an empyema due to improper surgical facilities.

If, however, the situation demands lifesaving action, as in the case of tension pneumothorax, a large caliber needle may be introduced into the pleural space at an angle to follow the curvature of the inner thoracic cage. The hub of the needle is then connected to improvised underwater drainage. If this type of drainage is not on hand, the hub is covered with a finger cut from a rubber glove. An encircling string tie will keep it in place. The tip of the "finger" is then cut off to produce a check valve—the air can leave the pleural space via the needle but cannot enter it since the rubber collapses. This simple device may well be lifesaving until definitive therapy is possible. Routine use of continuous needle drainage in preference to tube drainage is not recommended, for the danger of lacerating the expanding lung is too great.

SUMMARY

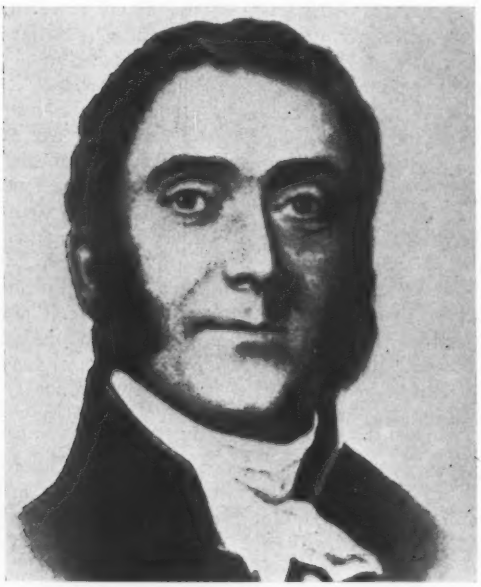
Spontaneous and traumatic pneumothoraces are best treated by inserting a drainage catheter of either a Robinson or mushroom type into the pleural space with constant underwater suction. In hemopneumothorax the use of a larger catheter, generally a No. 34 to 38 French, is mandatory when proper facilities are available for its insertion and supervision. In massive hemopneumothorax an open thoracotomy may be required.

For tension pneumothorax, simple needle drainage with a fashioned check valve may enable transportation of the patient to areas where definitive closed thoracotomy may be safely carried out.

Our Surgical Heritage

D. P. HALL, M.D., *Surgical Department, University of Louisville, Louisville, Kentucky*

UNITED STATES OF AMERICA



VALENTINE MOTT

VALENTINE Mott was born at Glen Cove, Oyster Bay, Long Island, on August 20, 1785, the son of Dr. Henry Mott and Jane Way Mott. He received his M.D. degree from Columbia College in 1806. Following his graduation he visited Europe and pursued studies in the hospitals of London where he became a pupil of Astley Cooper, Abernethy and Cline.

In 1809 he returned to New York and was made professor and chairman of the Department of Surgery of Columbia College where he remained until 1813, after which he occupied the professorship of surgery in the College of Physicians and Surgeons. Upon the establishment of the medical department of the University of the City of New York in 1840, Dr. Mott was

elected professor of surgery and president of the faculty, retaining these positions until 1850 when he resigned and embarked on an extended trip abroad.

In 1817 Dr. Mott was made attending surgeon of the New York Hospital and it was here that he performed most of his brilliant operations. Like his teacher in London, Astley Cooper, he was also a pioneer in vascular surgery. He ligated the innominate artery for the first time in the history of surgery in 1818. He successfully ligated the common iliac artery at its origin in 1827; in 1829 he ligated the carotid artery. In 1833 he ligated both carotid arteries simultaneously and in 1837 the right internal iliac artery.

The resignation of Dr. Mott as attending surgeon of the New York Hospital was accepted in 1837. He was appointed consulting surgeon and continued in this position until his death on April 16, 1865.

EURÓPE

BARON DOMINIQUE JEAN LARREY

DOMINIQUE Jean Larrey was born on July 8, 1766, in Beaudean, a small village in France, noted since the time of the Romans for its medicinal waters. He was educated by his mother and a parish priest, Abbé Grasset. After the death of his father in 1779, Larrey, a lad of thirteen, was sent to live with an uncle, Alexis Larrey, chief surgeon at a large hospital and quite a successful surgeon in Toulouse. Under this splendid guidance Larrey first finished the course in the College of Esquile and then attended the Toulouse School of Medicine and Surgery.

In 1787, after having studied under Louis and Desault in Paris, he passed the examination and was appointed auxiliary surgeon in the Navy and ordered to proceed to Brest. It was during this time that Larrey organized the junior surgeons at Brest into a study group and lectured to them on surgery and anatomy. During this year he saw his first active service on the "La Vigilante," and on his return to Paris he was made second surgeon and intern at the Invalides.

In 1792 Larrey joined the French stationed at Strasbourg as an Army surgeon. It was here that he first advocated the use of flying ambulances to evacuate the wounded under enemy fire. In 1812 Larrey became the first surgeon of the Grande Armee with which he took part in about 400 engagements. He was wounded three times and it is said that he performed as many as 200 amputations in twenty-four hours at Borodino.

Larrey's great devotion to Emperor Napoleon is well known but it is not well known that Napoleon said of Larrey, "*c'est l'homme le plus vertueux que j'aie connu*"—that he was the most virtuous man he had ever known. This from Napoleon was quite a compliment.

Larrey's contributions to surgery were many, such as the use of salt solution in simple wounds and the use of Labarraque's solution in case of infected wounds; the avoidance of all ointments or elaborate dressings; the avoidance of all meddlesome surgery; the resection of ribs for empyema; the supporting treatment of burns; immediate amputations; the removal of the wounded to a base hospital as soon as possible; flying ambulances. His "Clinique Chirurgicale" published in 1829 was a vivid account of military surgery and his "Memoirs" were most widely read. Larrey died in 1842.

Book Reviews

Surgery of the Chest. By Julian Johnson, M.D., D.SC. (Med.) and Charles Kirby, M.D. Second edition. Year Book Publishers, Inc. Chicago, 1958. *Price* $9.75.

This edition is a well written and well illustrated reference book of operative technic. It will be of primary value to students of medicine and nursing, and to the resident surgeon. The thoracic surgical procedures presented are those used by the authors but represent, with minor technical variations, accepted methods of treatment. This is not a complete textbook of thoracic surgery since clinical, radiological and pathological discussions are avoided. However, a section on diagnostic studies is included which stresses the importance of history, physical examination, laboratory tests and radiological examination in the evaluation of the patient.

This edition differs from the first primarily in the amplification of the section on cardiovascular surgery to include the more recent developments in this field. The original discussions of patent ductus arteriosus, coarctation of the aorta, tetralogy of Fallot and pulmonary stenosis are rewritten. The section on mitral stenosis is expanded to include the right and left transpleural approaches to the mitral valve. Sections on open heart surgery, atrial septal defects, ventricular septal defects, other congenital lesions, aortic stenosis and aortic aneurysms are added to the chapter on cardiovascular surgery. In the review of open heart operations both hypothermia and cardiac bypass using extracorporeal circulation are considered, and illustrations are added to delineate the uses of these technics.

Many changes are made throughout the book to incorporate advances in surgical procedures that occurred after the publication of the first edition. Also, some illustrations are changed to show the application of new methods and of recently developed instruments.

NEIL C. ANDREWS, M.D.

The Roosevelt Hospital 1871-1957. By the Committee on the History of Roosevelt Hospital. New York, New York.

This is a handsome, beautifully printed and illustrated volume of 300 pages compiling the history of a hospital that has played a notable role in the development of American medicine. It is readable and presents with candor the many-sided human experiences that make an institution venerable, from early nursing services through war experiences. Its early staff included men eminent in medicine: William S. Halsted, Hans Zinsser, Charles McBurney and many others. For many years it was the principal teaching hospital of Columbia's College of Physicians and Surgeons, and still enjoys a close association. The volume holds interest not only for Roosevelt's alumni but also as a rich historical source and a fascinating account of the vicissitudes inherent in building an American medical center.

DAN W. ELLIOTT, M.D.

Ideals in Medicine. Edited by Vincent Edmunds, M.D., M.R.C.P. and C. Gordon Scorer, M.B.E., M.D., F.R.C.S. The Tyndale Press. London, 1958.

This book has been written to represent the findings of a study group. Its aim is to present the distinctively Christian ideals as they may be employed in the service of medicine. The format consists of individual chapters written by a physician or physicians representing most of the medical specialties. Although not all the chapters are of equal merit, I believe the editors achieved their avowed purpose.

The group believes that the relationship between the physician and patient or the physician and colleagues is not stressed sufficiently in the physician's training. In the instances when "ethics" or "etiquette" is touched upon, it frequently is done on the basis of outmoded codes. The various chapters therefore present current concepts of the Christian approach to the various problems besetting the physician.

The problems of euthanasia, personal standards, what to say to the patient, professional secrecy, research and ultimate loyalties are well presented.

The essence of the book is contained in two quotations. One is by Lord Lister: "The one rule of practice is to put yourself in the patient's place." The second quotation, from which the first was probably derived, is from the Bible: "Whatever you wish that men would do to you, do so to them."

RICHARD J. IRETON, M.D.